Index Number

Vol. 223 No. 6 JUNE, 1952 No. 962

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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Frank B. Block, Franklin G. Ebaugh, John E. Gordon, E. G. D. Murray, Irving J. Wolman
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**Geriatrics: Past, Present and Future.** By O. H. Perry Pepper, M.D. 589

**Bacterial Susceptibility to Antibiotics.** By George M. Eisenberg, D.Sc., and Bernard M. Wagner, M.D. 600

**Comparison of a New Step Test with a Treadmill Test for the Evaluation of Cardiorespiratory Working Capacity.** By George E. Welch, M.D., Robert A. Bruce, M.D., William C. Bridges, M.D., A. Dean Johnson, M.D., J. H. Lehmann, M.D., Marie Nielsen, R.N., and David Glenn. 607

**Study of the Mercurial Diuretic, Thiomerin (Mercaptomerin), by Subcutaneous Injection in Patients with Congestive Failure, With Special Reference to Local Reactions.** By Harry Gold, M.D., Theodore Greiner, M.D., Sydney B. Mathes, M.D., Raymond R. Marsh, M.D., Leon J. Warshaw, M.D., Walter Modell, M.D., Nathaniel T. Kwit, M.D., Harold L. Otto, M.D., Solomon Garb, M.D., Hyman Bakst, M.D., and Milton L. Kramer, M.D. 618

**Plasma Iron: Normal Values; Response Following Medication.** By Willis M. Fowler, M.D., and Adelaide P. Barer, Ph.D. 633

**The Use of Red Cell Mass in Rheumatoid Disease.** By Mark W. Garry, M.D. 642

**Rheumatic Fever During the First Few Years of Life and Its Differentiation From Endocardial Fibrosis.** By R. Bruce Logue, M.D., and J. Willis Hurst, M.D. 648

**The Use of a Cation Exchange Resin in the Management of the Fluid Retentions of Normal and Toxemic Pregnancies: Further Observations.** By W. Robert Penman, M.D. 657

**Evaluation of the Effects of Khellin on the Human Electrocardiogram.** By William H. Button, Jr., M.D., and Charles C. Foote, M.D. 663

**Ventricular Rate Response Following Exercise During Auricular Fibrillation and After Conversion to Normal Sinus Rhythm.** By Donald G. Wetherbee, M.D., Morton G. Brown, M.D., and Daniel Holzman, M.D. 667

**Progress of Medical Science**

**Pediatrics—Hypertension in Children: A Review.** By Wallace W. McCrory, M.D., and Frank W. Nash, M.D. 671

**Gynecology and Obstetrics—Diabetes Mellitus and Pregnancy with Special Reference to Fetal and Infantile Loss.** By Carl Bachman, M.D. 681

**Proceedings of the Physiological Society of Philadelphia** 694

Complete contents on adv. page 10

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1952

## ORIGINAL ARTICLES

# GERIATRICS: PAST, PRESENT AND FUTURE*

By O. H. Perry Pepper, M.D.

EMERITUS PROFESSOR OF MEDICINE, UNIVERSITY OF PENNSYLVANIA
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**Past.** The Greeks divided life into 4 periods and as usual the Greeks had a word for each. A child was a *pais* from which we derive our term pediatrics, then one became an *ephebos*, then an *aner*, and finally an old man was a *geron* from which the term geriatrics comes. The other part of the word is derived from the Greek, *iatrike*, which meant medical treatment. Another term, gerontology, is also used today, but seems to be less popular, although it has a wider meaning, for it implies all knowledge about the aged and is not limited to the medical aspects of the subject.

It was not until 1914 that the word, geriatrics, came into use, as a result of the publication in that year of the first textbook entitled "Geriatrics" by Nascher. Since then, this subject has come very much to the fore and today there are special journals and societies in this field, and much interest is being shown and research done.

This does not mean that there was no interest in old age prior to this century, but it was not organized or scientific. In fact, it is interesting to find that most of the interest centered about longevity rather than about the medical problems of the elderly. And secondly, the many infirmities of old age were taken for granted and accepted as inevitable and irremedial. Both of these points of view discouraged any progress in what today constitutes geriatrics.

Longevity has, of course, interested both laymen and physicians from the days of Methuselah to the present. Unfortunately, the records of long life are notoriously inaccurate: sometimes from ignorance; sometimes from deliberate exaggeration for gain, or because the very old are proud of their age. Some of the reports of great longevity have arisen through the error of adding together the life span of two individuals of the same name, as was done in the instance of the supposedly very long lived Countess of Desmond. This Countess Katherine was reputed to have lived from 1464 to 1604 and to have had a daughter at the age of 65, and a second set of teeth shortly before her death. Actually, the lives of 3 different countesses were united into 1

* The Fourth Annual John H. Musser Lecture, presented at Tulane Medical School, November 30, 1951. Dr. Musser was Assistant Editor of the American Journal of the Medical Sciences from 1915 to 1922, and Editor from 1922 to 1924.

in her. Better accredited instances of great age, however, are not rare; the most interesting from a medical point of view being that of Thomas Parr, who, believe it or not, is credited with having lived during the reigns of 10 British sovereigns and died at the age of 152. His post mortem examination was performed and carefully recorded by the great Thomas Harvey, the discoverer of the circulation. He found the organs in remarkably healthy state and ascribed the death to plethora from the luxurious living in London, where Parr had been brought to see the king. Harvey was canny enough to state on the frontispiece of his report that "other of the King's physicians being present." The gravestone of Thomas Parr testifies to his long life.

Much speculation has been centered on the factors which may predispose to longevity, but with little result. Unfortunately for the moralists, neither alcohol, tobacco, or sexual excesses seem to influence the matter very much. As Benjamin Franklin wrote in his Poor Richard's Almanac, "one sees more old drunkards than old doctors". The one primary requisite for a long life is a good circulation, and in this, one perhaps finds the explanation for the distinct influence which heredity plays. As Osler put it, "Choose your parents carefully if you would live long". Osler remarked that much depends "on the quality of arterial tissue (vital rubber) which the individual has inherited". Some of the physiologists today admit that a something called "hereditary constitution" is a factor in the life span of the individual.

Today we see no great increase in the number of instances of extreme old age, but it is certain that a far greater percentage of the population live to reach the age of 60, 70, 80 and over. Statistics are available to prove this fact beyond any possible doubt. For example, there are today over 7,000,000 Americans living above the age of 65, and 1,000,000 over the age of 80. This is a 30% increase during the past decade. Many more figures could be quoted, but statistics are not needed to prove what every one knows.

Although the emphasis on longevity may have delayed a realization of the importance of geriatrics, it is this very fact of the increasing elderly population which has in recent years stimulated a keen interest in the medical problem of old age. Geriatrics has as its primary objective, not merely to prolong life, but to improve the state of health with which man arrives at old age, and to improve the diagnosis and treatment of the so-called infirmities of old age and the diseases which occur in the elderly. No one wants to live long unless his health is at least reasonably good.

The second factor which seems to have delayed the rise of geriatrics was the acceptance of all the infirmities of old age as an inevitable and so to speak normal part of the aging process. Much was written in very ancient times of the changes which appear in old age. Cicero and Shakespeare, among others, discussed this matter, but to me the most fascinating presentation is found in the Bible in the 12th chapter of Ecclesiastes. This is the familiar chapter which commences: "Remember now thy Creator in the days of thy youth, while the evil days come not, nor the years draw nigh, when thou shalt say, I have no pleasure in them".

In the succeeding verses the various infirmities of old age are detailed in the highly symbolic allegorical language, so often met with in ancient Semitic writings. The true meaning of these verses has been known for many years, but they are still often read today

without any understanding of their real significance. The first full and clear interpretation was that by John Smith in a book published in 1666. He points out, for example, that the third verse which reads, "In the day when the keepers of the house shall tremble, and the strong men shall bow themselves, and the grinders cease because they are few, and those that look out of the windows be darkened", clearly refers to well known infirmities.

The words, "the keepers of the house shall tremble" refers to the tremor of the hands of the old; the legs are the "strong men which bow themselves"; the "grinders cease because they are few" is a clear reference to the loss of teeth in old age; and the "windows", the eyes, are darkened by senile cataract.

In further verses, we find that the early awakening aged "rise up at the voice of the bird"; they are "afraid of that which is high" because they are timid and suffer from dizziness. Read this chapter again and discover for yourself the meaning of its beautiful allegories. To help you, let me remind you that the phrase the "Almond tree shall flourish" refers to the greying of the hair, and that "the grasshopper shall be a burthen" has had many interpretations, of which the correct one is, that which gives the meaning of male sexual organ to the word "grasshopper". Surely this would be well described in the old as a burden. And so the next phrase, "desire shall fail" because "man goeth to his long home".

It must be admitted that the meaning of certain parts of this chapter is not entirely clear. Some do not agree that the verse which reads "And the doors shall be shut in the streets, when the sound of the grinding is low" should be interpreted as a reference to the constipation which may result from inadequate chewing. Even more controversial is the verse, "Or ever the silver cord be loosed, or the golden bowl be broken, or the pitcher be broken at the fountain, or the wheel broken at the Cistern". The silver cord has been translated as the spine or as the spinal cord. Most amazing of all, however, is Smith's interpretation of the final words. He translates "pitcher" to be the veins; the "fountain", the right ventricle; the "wheel", the arterial circulation, and the "cistern", the left ventricle. This would imply, as Rolleston writes, "That King Solomon was perfectly acquainted with the circulation of the blood discovered by William Harvey in 1616". But whatever the meaning, we now know that Solomon did not write the Ecclesiastes.

Shakespeare's works contain many references to old age, but it must be remembered that in that Elizabethan era, aging came quickly and few lived long. In his earlier writings, it is the physical features of old age which he mentions, often with little sympathy. In "As You Like It", one finds the justly famous description of the ages of man.

As he himself aged, his interest centered more on the psychological aspects of senility and it has been said that the picture of Lear's mental infirmities is a picture of his own, although Shakespeare was but 40 years of age when King Lear was written.

As time passed, there appears in the literature an effort to list the diseases characteristic of old age, as distinguished from the expected infirmities of the elderly. The great French neurologist, Charcot, for example, listed senile marasmus, senile osteomalacia, senile atrophy of the brain, alterations of the blood, senile asystolism and arterial atheroma. Also we encounter an early recognition of what we ought to do about the aged. In 1905, Metch-

nikoff, who attributed our early decay to poisons from the intestinal flora, discussed in a fascinating lecture the custom of certain savage peoples of killing off their aged.

As we continue to follow geriatric thought, we next meet efforts to distinguish senescence from senility, senescence being used to indicate the normal or physiologic changes of the aging process; senility those due to actual pathological processes. This matter is still far from clear and as our knowledge increases, there is a tendency for us to discover that there is a sound pathologic explanation for some of these so-called senescent changes, such as graying of the hair and loss of teeth. The future may prove that many are avoidable, or at least greatly postponable. For the present, however, we must still accept many changes as physiologic, and it is important to distinguish them from the results of disease. We will return to this thought when we come to geriatric diagnosis.

Physiologic aging or senescence implies many changes: some loss of height and weight, osteoporosis of bones and atrophy of cartilage. Always there occurs progressive atrophy of all lymphoid tissue and of most of the parenchymal organs. The tonsils and lymph nodes tend to an early reduction in size and obviously the significance of the finding of even slight enlargement of such structures is far greater at 80 than at 8. Atrophy lessens the weight of the spleen, liver, kidneys, thyroid, brain, and in fact of almost every organ except the heart. Only the nose and the ears continue to grow. Emphysema is the rule in the lungs and calcification of the media of the larger arteries is so common as to be considered physiologic, but this so-called Mönckeberg's sclerosis is a very different process from the pathologic forms of arteriosclerosis.

In order properly to recognize the pathological changes of disease in the elderly, in other words senility or abnormal old age, we must obviously be familiar with the changes to be expected at the age of our patient. The pediatrician well knows this need: he knows the normal rate of growth, the date of the closure of the fontanelles, the relative changes in visceral size, the normal speed of mental development. The pediatrician uses this knowledge of the normal as a base line, and in the diagnosis of disease employs only findings which deviate from the known normal. In geriatrics, we must try to do the same, although it is far harder than in the pediatric field. The aging individual presents increasing changes of senescence, and these being in the same direction as those of senility, it is often very difficult to distinguish the one from the other. Nor is there any strict time schedule for senescence which would enable us to say in a given individual that such and such changes were appearing so early as to constitute senility rather than senescence.

**Present.** This brings us up to what I choose to call the present era of geriatrics, although there is obviously no clear line of demarcation. Nor is there any date which can be affixed: perhaps 1914, when Nascher's text book appeared, is as good as any other.

In the past few decades every branch of medicine and medical science has been busy studying and gathering data concerning the involutionary process and the diseases of the old. Let us glance briefly at some of these fields.

ANATOMY. Anatomical observations have confirmed the constancy and importance of involutional atrophy in the

aging process. It has become known that this atrophy, although constant and wide spread, does not affect the various organs to the same degree. For example, the ovaries exhibit a great loss of weight; the testes much less, while the weight of the thyroid, adrenal and brain change even less. This latter is surprising in view of the functional deterioration of the mind so often seen in the aged, but it is probably due to the large amount of stroma in the brain which maintains the weight of the organ and hides the severe atrophy of the parenchyma. Furthermore, the picture of parenchymal atrophy is not the same in every organ. In other words, it is not quite correct to speak simply of atrophy as the whole explanation of senescence. Also, there are always present in the aged, organ changes due to pathological processes which confuse the issue and bring us back face to face with the distinction between senescence and senility. We will meet this problem again when we discuss the significance of osteoporosis of the old.

Physiology and Chemistry. It is tempting to think of atrophy due to wear and tear as the primary process and all functional changes as secondary to the parenchymal atrophy. This is too easy and is not the whole truth. In fact, it may well be that the structural atrophy will be found to arise from reduced tissue oxidation, altered cellular chemistry with pigmentation and fatty infiltration, and tissue dessication. This is not merely of academic interest, for, if the whole story were known, more might be done to delay this process which today we accept as physiologic.

Whatever the cause or causes of the parenchymal atrophy, the result is reflected in the reduced functional capacity of those organs in which the atrophy is severe. For example, a third of all those over the age of 60 exhibit an absence of hydrochloric acid in the gastric secretion, a fact of importance in medical diagnosis and treatment. As a rule, the lessening of functional capacity does not, in the absence of coincident disease, reduce the ability of various organs to meet the needs of the aged body under normal conditions. However, the margin of safety is greatly narrowed in age and any increase in stress or strain may place a demand on one or other organ which cannot be met.

So little is known of the biochemistry of aging that it offers a wide opportunity for investigation. The blood both hematologically and chemically reveals no important changes as age advances. Nor does the chemistry of the body by the methods usually employed. Isolated reports do mention a few deviations such as, for example, a depression of the glucose tolerance test as age increases. Also the enzyme activity is said to be decreased and intracellular calcium to be increased. But no broad alterations are found; more knowledge is needed.

Pathology. The pathologist has long appreciated that certain generalizations apply to the aged. He is sure to find the usual changes of old age in addition to the evidence of whatever disease or diseases may have occurred during life. The results of wear and tear, of injury and of previous disease may be evident and may confuse the total picture.

As a rule, the old organism is damaged goods to a degree unsuspected until all is revealed to the pathologist. Frequently, there are multiple diseases present, no one of which, sometimes, can be named as the cause of death. Each has contributed to the breaking down of the already narrowed margin

of safety of the circulatory system perhaps, or of the kidneys.

Several distinct and unrelated neoplasms which have been symptomless during life may be discovered, for even the carcinomata are characteristically slow growing. The pathologist can demonstrate the reason for this behavior. He also finds the lessened cellular reaction of the body to infection which is recognized by the clinician in the tendency of the aged to have less leukocytosis and fever.

Of all the many pathologic processes which may plague us in middle age, there are relatively few which may not occur in the elderly; even the so-called diseases of childhood, such as pertussis, may occur or recur in old age. Sir William Jenner, of smallpox vaccination fame, had an attack of whooping cough when over 65 years of age. He recovered, contrary to the usual fatal effects of this disease in the elderly. Of course, the degenerative diseases dominate the picture: arterial disease, emphysema, diverticuli of the sigmoid and esophagus, and others are frequent.

Lists of the leading causes of death show marked changes in the past 50 years, but are often inaccurate unless based on autopsy statistics. Tuberculosis has fallen from the top of the list; heart disease has taken its place. Pneumonia and diphtheria, for obvious reasons, have dropped, and those who would have died of these and other acute conditions, now cured by antibiotics, surgery, or otherwise, have lived to die of cancer or the degenerative diseases. Lobar pneumonia, once "the old man's friend", is now seldom seen at the post-mortem table. Thus the pathologist is able to evaluate the results of better clinical diagnosis and treatment: the influence of specific therapy, of better surgery, of better nutrition and of the good and the evil impacts of our changing civilization.

This very brief survey of these basic subjects is not by any means an adequate statement of the amount of information which is available in the wide field of gerontology. However, it must be admitted that the results of research in geriatrics have not as yet been as illuminating, nor of as much practical value, as one might hope.

Let us now turn to the clinical side of the subject. At once we encounter certain clinical phenomena characteristic of disease of the old, which are the manifestation in life of peculiarities already mentioned in the pathology found in this group. The aged patient is damaged goods; has atrophies and senescent changes appropriate to his age, has narrowed margins of safety in many directions and is apt to have multiple pathologies. All of this must be appreciated by the physicians, surgeons, or specialists, for this enters into the problems of diagnosis and of therapy.

Furthermore, the doctor must be aware that diagnosis is often difficult in the aged because of an absence of many of the usual signs of disease. As Sir Humphrey Rolleston put it, "the organs suffer in silence without any local or general disturbance, though collapse may occur". Gall stones may pass through the ducts into the bowel with little or no pain. This obtunding of pain is one of the few blessings of age.

Fever and leukocytosis may be absent or slight, even in severe infections. Physical examination, therefore, becomes of even greater importance. Many a doctor has been humiliated when the autopsy has revealed a lobar pneumonia in an old person who had seemed merely to fade out without cough, pain, fever or leukocytosis.

Also the physician must be alert to

interpret the case in which the evident difficulty is an organ failure, cardiac or renal, for example, but the underlying cause of this failure is some silent infection which has over-balanced the already narrowed margin of safety of this organ. Homeostasis in general is less well maintained.

Every medical man must know that almost every disease may occur in patients of advanced age, but he must also know that some are found more frequently than others, and may vary somewhat in their behavior from the picture usual in other age groups. Many diseases, however, differ in no respect from the same process in middle age.

If anyone wants statistical data on the incidence of disease in old age, they can be found in a recent book by Monroe* giving an analysis of 7941 individuals over 61 years of age. Time does not allow me to quote his interesting findings.

With this background it is easy to see that geriatric diagnosis may at times be difficult unless certain facts are known to the physician. Let me mention three actual cases:

**Case Reports.** CASE 1. A male of 77 was found to have a severe anemia with a color index approaching 1 and no change in white cells or platelets. The history and symptoms did not help and the physical examination was negative except for hemorrhoids and an absence of Achilles reflexes and of vibratory sensation below the knees. There was no free hydrochloric acid in the gastric secretion. Roentgenograms of the gastro-intestinal tract revealed atrophy of the gastric mucosa, while the bone survey showed generalized osteoporosis. In a younger person the change in vibratory sense and the absence of hydrochloric acid could have been used to bolster a diagnosis of primary Addisonian anemia, but not at age 77. The osteoporosis might suggest metastatic cancer and the achlorhydria would occur in carcinoma of the stomach, yet both osteoporosis and achlorhydria are seen in senescence. Many other studies were made, but a diagnosis still was not. Finally, at long last it was appreciated that there was more bleeding from the hemorrhoids than had been suspected. When this was stopped by surgery, the anemia began to respond to medical therapy. A slight but long continued bleeding had been enough to exhaust the elderly bone marrow. He was discharged cured, still without vibratory sensation in his legs or hydrochloric acid in his stomach and with osteoporosis.

CASE 2. An elderly mayor of a nearby town was taken acutely ill with pain in the lower left abdomen; there was fever, rigidity, tenderness and a mass. At a consultation with some half-dozen doctors, I made the diagnosis of diverticulitis of the sigmoid, which is common in the old and often gives this picture. I stated that this was often called "the left-sided appendicitis of the elderly" because of the similarity of all the symptoms. I do not believe the doctors were listening very carefully, for when at operation a ruptured appendix with an abscess localized in the left lower quadrant was found, I received many queries as to how I had made such a brilliant diagnosis. At first I tried to explain that I had been wrong, but soon I decided that doctors so often fail to get credit when they are right that I might as well take what I could get when I was wrong.

Lastly, a case in which I was right.

CASE 3. Another male, aged 61, came for a second opinion, having been diagnosed as severe chronic glomerulo-nephritis in another city. He was very anemic with 2.5 million red cells, hemoglobin 53% and obviously weak and ill. The physical examination was negative except for pallor and the evidence of loss of weight. The blood pressure was not elevated, in fact only 116 over 60. Urinalysis was that expected in glomerulonephritis with fixed low specific gravity, and the impaired renal function was reflected in the low phthalein excretion and in a consistently high blood urea nitrogen and creatinine. All tests of kidney function revealed marked impairment. Already diagnosed after study in another University Hospital and with the evidence I have detailed, it would have been only too easy to agree with the previous diagnosis.

On the other hand, chronic glomerulonephritis is remarkably rare in age, his blood pressure was normal, his eye grounds fairly healthy. Most cases of this type of nephritis develop it in time to die of the disease before old age is reached. Also there is one

* Monroe, Robert T. "Disease in Old Age." Harvard University Press, 1951.

disease, multiple myeloma, which is frequent in old age and especially, in my experience, in males and which occasionally gives a picture simulating chronic kidney disease. The fortunate remembrance of this led to a bone marrow examination; a positive diagnosis of multiple myeloma, although the roentgenologic bone survey was negative. A polite letter from me to my friend in the other University telling him I was sure he would like to know the correct diagnosis and by inference, his own mistake, was of course dispatched. I have more than once been on the receiving end of this type of correspondence. In fact, any time you think you have a new feather in your cap, someone usually comes up and pulls a feather out of your tail.

So much for geriatric diagnosis. Basically, it is identical with the usual medical procedure, but there are some peculiarities which must always be kept in mind. Now let us turn to treatment.

THERAPY. Therapy of the aged, along with treatment in general, has been greatly improved in recent years as a result of a better appreciation of the special problems presented by this group of patients. Certain generalization can be made: drug therapy is often disappointing, nursing and detailed care are of the utmost importance, and surgery is borne better than one might anticipate.

Drugs may give unexpected and unfortunate effects due in some instances to slow absorption, in others to slow elimination with resulting cumulative action. It has long been known that morphine may cause excitement, delirium and dangerous depression of the respiratory center. In fact, none of the sedatives can be counted on for their usual action. Belladonna, even in small doses, may produce delirium and cumulative action is common. The sulfa drugs are tolerated less well by the old. Digitalis often fails to produce the full expected result in persons of advanced age. All of this can be interpreted in terms of what we know of the reduced efficiency of various organs: lessened renal function, slowed absorption from the gastro-intestinal tract, for example.

Also we have learned that good nursing is of greater value than in younger adult patients. The aged have long-established habits which must be respected: a man who has not slept more than 5 hours a night for a quarter of a century may be harmed by the efforts of a doctor to give enough sedative to ensure 8 hours. The diet habits must not be changed too abruptly, nor should a patient's habitual intake of alcohol, if reasonable, be too sharply reduced. Remember it has been said, "Wine is the milk of old people". The old need quiet and gentleness; they can be killed by exhaustion from a too rapid and enthusiastic diagnostic study. Such a schedule as: 6 a. m.: enema; no breakfast; 10 a. m.: gastro-intestinal roentgen-ray; 2 p. m.: return to roentgen-ray department, and so on, with blood counts, electrocardiograms and others thrown in. Autopsy 2 days later failed to reveal cause of death. Too active treatment is also often harmful.

In sharp contrast to what has just been said, the surgeons and anesthetists have taught the medical men that major surgery is possible on patients of very advanced age. Not so many years ago, the internist feared to permit surgery and temporized too long; now he is quick to seek surgical help. This has resulted not only from better surgical techniques, but from far better preoperative preparations, better anesthesia, early ambulation and careful postoperative control of fluids, electrolyte balance, nutrition, anemia, rest, and others.

The literature is full of reports of successful major surgery in the old, such as gastrectomy at 96. But the prize report to my mind is that of Everidge

in England, whose 95-year old patient refused to have his obstructive prostate removed unless Everidge would repair his hernia at the same operation. The surgeon asked why he was not satisfied with the effective truss he was wearing. "It interferes with my golf," was the reply. So both the prostate and hernia were successfully taken care of at one time. It is no wonder that with that vital spirit the patient had reached the age of 95.

In my opinion the advance in geriatric surgery is the most important contribution which has resulted from the centering of attention on the diseases of the old. Only a few years ago a high percentage of elderly men with prostatic disease were judged to be unsuitable for surgery, but in a recent series of 35 men over 80 years of age, reported by Taylor, no case was refused. Although the ages ran up to 92 and the heart was diseased in over half, the mortality was only about 3%. Similar encouraging reports have appeared in other fields of surgery. Apparently, modern methods make surgery possible in the aged even in the presence of what one may call the aged heart.

Of course the interest centered during recent years on the medical problems of the aged has led to advances in every branch of medicine. We have touched on medical diagnosis and treatment and on surgery: we cannot discuss all the others. We must, however, mention one which seems to me to be of great importance: the change in our attitude toward the psychologic and psychiatric aspects of old age.

Again we find that in the past the mental deterioration of the old was accepted as an inevitable part of normal senescence. When grandfather reached his anecdotage, his oft repeated stories were suffered in silence. Again, there was a distinction drawn between senescent phenomena and the senile dementias, but nothing much was done about either.

Today it must still be admitted that mental changes of one kind or another are present in many aged persons. In Monroe's group of almost 8,000 aged, only 41% were considered to have a normal mental and nervous system status, and many more were thought to exhibit maladjustments of one kind or another, such as a withdrawal from normal performance. More than a third of his whole group showed a psychoneurotic reaction, sometimes arising from the tragedies of life: the deaths of dear ones and the resulting loneliness, the loss of occupation with its ensuing boredom, and the loss of financial independence. In another large group, however, the mental change was a toxic-affective psychosis induced by cardiac, renal or other disease.

Today a great deal is being done about both those groups and the physician has a new responsibility and opportunity. The conscientious, sympathetic doctor can help by encouragement, by finding new activities, civic service or hobbies for his patients. There is a wide movement now-a-days to keep the elderly active and interested in something, to keep them employed longer, to join them in social groups, to give opportunities for participation in hobbies of any kind, from art to zoology; in fact, anything. The mental deterioration is not always hopeless, if an interest in life or a sense of usefulness can be supplied. Even an advanced case, such as myself, can be helped by being allowed to give a talk on one of his interests.

In the other group, the important thing is the realization that many psychic disorders of old age are not primary, but secondary to disease of organs other than the brain. Here we

turn back to the new therapies now available for treatment of these diseases by vitamins, antibiotics, replacement therapy and surgery. Many a case too casually diagnosed "senile dementia" has vastly improved when proper treatment of a failing circulation was instituted.

This brings us to the question of prevention of the so-called ravages of old age. There can be no doubt that as medical care improves in childhood, adolescence and maturity, man should reach old age in far better shape; he will always be damaged goods, but far less damaged. As this goes on, we will learn much about the supposed inevitability of the senescent changes. Good dentistry may prove we need not so soon lose our teeth; good nutrition may help postpone grey hair; arteriosclerosis may be delayed. If man is thus kept healthy in every manner and his actual diseases are diagnosed and treated in time, the problems of geriatrics will be greatly changed. An increasing number will reach old age and the span of life may be lengthened, but more important than this is the hope that those who do survive to old age will be healthier, happier and more useful.

At this point a warning must be interjected. As a result of new therapies, cases of such diseases as pernicious anemia, diabetes, and hypothyroidism are kept alive and well to reach old age. These therapies have not been in use long enough for us to know what may eventually occur. We have had insulin some 30 years and reports are hinting that in spite of proper treatment, we must be alert for troublous developments. Also we must be quick to realize that other diseases may and will appear in these patients, and we must not insist that new symptoms are due to some return of the long standing chronic disorder. I have seen an elderly man with pernicious anemia under effective liver treatment develop anemia again. It was assumed that this indicated some fault in treatment and time was wasted before the silent carcinoma was discovered. In this group of patients, we may be about to see some new syndromes.

Death will still be at the end of the road. The doctor always loses the last battle, but he can do much for his dying patient and for the family in their time of sorrow. The aged often fear death but little, if at all. As the great William Hunter said, "If I had strength enough to hold a pen, I would write how easy and pleasant a thing it is to die."

**Future.** And now what of the future of geriatrics? There can be no question that much has been accomplished by the increased interest in this field during recent years and I hope my remarks have made this point. But should geriatrics continue as a limited field of interest? Should it become an actual specialty analogous to pediatrics?

There are some who would answer these questions in the affirmative and would point out what has already been achieved by the focusing of interest on the problems of the aged. They would stress the value of the special journals, books and societies on this subject and would prophesy continued progress. They would draw many analogies with pediatrics: the need of special knowledge, the establishment of a base line for senescent changes. They might even advocate a special service and wards for aged patients in hospitals.

Those opposed would emphasize that aging is a highly irregular process and that there can be no such base line of aging as there is of growth in childhood. They would point out that the adult advances imperceptibly into

old age and that actually no one can say at what age one becomes old. Most of us think of old age commencing 10 years ahead of our present age.

It is interesting that Dr. Edward J. Stieglitz, one of the leaders in this field and who has published with collaborators by far the best book on this subject, writes that "Geriatric medicine is not a specialty" and he hopes it will not become one. Note that he avoids the use of the word geriatrics as a noun, using it as an adjective in the title of his book, "Geriatric Medicine." This is an important difference in emphasis.

To me also, it seems that the care of the aged belongs to the physician and to the specialists in every branch of medicine. I suspect that as we learn more about the healthy and diseased aged, the present trend toward making geriatrics a specialty will come to an end.

It would seem, therefore, that our review of geriatrics reveals that it was neglected in childhood, has grown into a healthy adolescence, but as is always true in prognosis, the future is uncertain.

But no matter how much scientific advance may be made in geriatric medicine, nor who has the care and treatment of the aged, this group of patients will always present a challenge to us of the medical profession. The aged and the dying still deserve our best efforts and our highest skill. They also need that sympathy and understanding which come from the heart. He who can meet this challenge must have the skill, the integrity and the heart, those qualities without which one can never reach the full stature of the physician. Such a man was John H. Musser, whom we honor tonight.

# BACTERIAL SUSCEPTIBILITY TO ANTIBIOTICS

## II. Determination by means of a standardized, routine procedure having clinical significance.

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and

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It is generally agreed that the selection of an antibiotic to be used in treating an infection be based on results of laboratory procedures which establish the identity of the infecting agent and its susceptibility to the various clinically useful antibiotics. While it may be feasible, and at times desirable, to delay antibiotic therapy in chronic infections pending completion of these studies, such a course is often inadvisable in acute fulminating infections. Here it is the diagnostic acumen of the clinician and his knowledge of therapeutics which govern the choice of an antibiotic. The many instances of dramatic clinical response seen in patients who have been treated with antibiotics selected without benefit of prior *in vitro* susceptibility tests are evidence of the fortuitous results obtained. Such experiences do not detract from the importance of these tests especially when we realize that: a) They furnish the data which form the foundation of the clinician's antibiotic sensitivity experience. b) They have established that among certain organisms, which as a group are considered to be susceptible to a particular antibiotic, there may be individual strains which are resistant to it. c) They have focused attention on the possibility that a bacterial strain, initially sensitive to an antibiotic, may develop resistance to it under appropriate conditions. d) They have shown that the selection of an antibiotic possessing maximal activity against a mixed flora cannot be made with certainty on clinical grounds alone.

There are available at present 2 types of susceptibility tests: the serial dilution test and the agar diffusion test. The serial dilution test is reliable and accurate in direct proportion to the effort which is made to insure constant conditions and adequate controls. This test is time-consuming, laborious and relatively expensive and therefore impractical as a routine procedure in a busy bacteriological laboratory. The importance of these factors increases in proportion to the number of antibiotics available for use. Consequently, a test which is easily performed and above all clinically significant, is desirable.

In an effort to fulfill these criteria, Bondi *et al.*[1] developed an agar diffusion test, utilizing filter paper discs as antibiotic reservoirs. In their procedure

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sterile filter paper discs of specified diameter are saturated with an antibiotic solution (penicillin or streptomycin) of known concentration and are applied to the surface of blood agar plates. These plates are then inoculated in a particular manner with a portion of a clinical specimen. Following an overnight incubation, the plates are examined for zones of growth inhibition surrounding the discs. In order to evaluate zone size in terms of concentration units, the diameter of these zones was compared with results obtained by streaking the same organism on the surface of agar plates containing known concentrations of antibiotics. Organisms were classified as "resistant", "moderately susceptible", and "very susceptible"; the dividing levels were selected on the basis of blood levels attained with ordinary dosages of the respective antibiotics used at the time. Bondi *et al.* were fully aware that this method would not yield values of inhibiting concentrations with the same degree of quantitative accuracy as those attainable by a well-controlled serial dilution test.

In our laboratory the Bondi procedure was studied by Wagner[5], who evaluated zone size in terms of minimum inhibiting concentrations as determined by a serial dilution test. He concluded that the method did not replace the more quantitative procedure for determination of inhibiting concentrations but was sufficiently reliable if the results were interpreted in terms of relative susceptibility.

As a result of the introduction of the newer antibiotics (chloramphenicol, terramycin and aureomycin) and in consideration of a changing concept of penicillin and streptomycin dosage schedules, modification and re-evaluation of the disc method seemed to be indicated. The purpose of this paper is to describe in detail the procedure used in our laboratory and to present our interpretation of the findings obtained with it. This method is the outgrowth of experience gained from several thousand disc evaluations which were made with satisfactory results to the clinician, the patient, and the laboratory.

**Materials.** Since the results of susceptibility tests are variable, depending upon the particular method used, we describe our procedure in detail.

A. Broth (for growing test organism).
   a. Bacto tryptose phosphate broth ..... 29.5 gm.
   b. Proteose peptone No. 3 ..... 10.0 gm.
   c. Distilled water q. s. ..... 1 liter
   d. pH adjusted 7.2. Dispense in tubes ..... 8-10 cc. per tube
   e. Sterilization at 120°C., 20 min.

B. Blood Agar (for susceptibility tests).
   a. To 1 liter broth above add
   b. PABA (2% ethanol solution) ..... 2.0 cc.
   c. Agar, granular, BBL ..... 20.0 gm.
   d. pH adjusted 7.2. Dispense in bottles or flasks in desired quantities.
   e. Sterilize at 120°C., 20 min.
   f. Cool agar to 45°C. and add aseptically sufficient sterile, defibrinated equine blood to a final concentration of 6%.
   g. Mix thoroughly and pour plates, dispensing 20-25 cc. of the blood agar to 15 x 100 mm. Petri dishes provided with porous porcelain tops. This volume of medium will provide an agar depth of 8-9 mm. Plates are dried for 1-2 hours or until free of surface moisture in an incubator at 37°C. with the lids partially removed.

C. Buffer Solutions.
   a. pH 6.0 (1%) dissolve 8.0 gm. $KH_2PO_4$ and 2.0 gm. $Na_2HPO_4$ in sufficient distilled water to make 1 liter.
   b. pH 7.8-8.0 (0.1M): dissolve 17.4 gm. $K_2HPO_4$ and 1.0 gm. $KH_2PO_4$ in sufficient distilled water to make 1 liter. The pH of these solutions is checked electrometrically. Sterilization at 120°C., 20 min.

D. Filter Paper Discs.

Discs of Whatman No. 2 filter paper, 6.5-7.0 mm. in diameter are cut with a suitable cork borer or paper punch and placed in petri dishes. These are sterilized at 170°C. in a hot air oven for 90 min. In situations where large numbers of tests are not anti-

cipated, it may be advisable for each dish to contain no more than 25-30 discs. Unused discs may be re-sterilized and used without fear of affecting results; however, repeated sterilizations in excess of two are undesirable because of the adverse effect produced on the absorptive qualities of the paper. We have found that our discs will absorb between 0.005-0.006 cc. solution when saturated as described below.

E. Antibiotic Solutions.

The potencies of the various antibiotics* used in our tests are:

a) Sodium benzyl penicillin ..... 1667 units per mg.
b) Streptomycin sulfate ..... 780 mcg. per mg.
c) Aureomycin hydrochloride ..... 1000 " " "
d) Crystalline chloramphenicol ..... 1000 " " "
e) Terramycin hydrochloride ..... 890 " " "

Table 1 shows the proper solvent for the various antibiotics and the concentration of the respective working solutions. These concentrations were selected in order that a saturated disc would contain antibiotic in an amount equivalent to the average blood level concentrations attainable in patients receiving specified dosages. For penicillin, streptomycin, chloramphenicol, aureomycin, and terramycin, these amounts are approximately 1.0 unit, 15, 15, 4, and 6 micrograms, respectively.

If sterile glassware is used in weighing the antibiotics and aseptic technique is employed in all subsequent steps in the preparation of the solutions, bacteriological filtration is not necessary. The solutions may then be dispensed in amounts of 2-3 cc. in sterile, pyrex tubes, and stored in a deep-freeze at −20°C. Under these conditions solutions maintain their potency for at least 30 days. Tubes for daily use are removed from the deep-freeze and allowed to thaw, and diluted if necessary to the desired concentration. By preparing 100 cc. amounts of each antibiotic solution once a month, and by handling these solutions as indicated, sufficient material is available for approximately 2000 tests per month. A test consists of one organism evaluated against one antibiotic.

Procedure and Interpretation.

1. Appropriate isolation media are inoculated with the clinical specimen. Following incubation, well-isolated colonies are "fished" to broth and incubated for 16-18 hours at 37°C.

2. A blood agar plate, prepared as described above, is streaked by means of a swab which has been dipped into a broth culture. Excess culture fluid is removed by gently pressing the swab against the walls of the tube. Streaking is begun at the top of the plate and continued with even, parallel strokes, until one half of the plate surface has been covered. Both the plate and the swab are now rotated 180° and the remainder of the plate streaked in an identical manner. A uniform, confluent growth will be obtained if the plate is now turned 90° and re-streaked with the same swab. Excessive pressure on the swab is to be avoided in order to reduce to a minimum the possibility of scratching the agar surface.

3. A sterile disc is picked up with a sharp, straight dissecting needle. The edge of the disc is brought into contact with the surface of the desired antibiotic solution and held there until the whole disc has become

TABLE 1

| *Antibiotic* | *Solvent* | *Concentration (units or mcg./cc.***) |
|---|---|---|
| Penicillin† | pH 6 buffer | 150 units |
| Streptomycin | pH 8 buffer | 3000 mcg. |
| Chloramphenicol | pH 6 buffer | 3000 " ‡ |
| Aureomycin | Sterile water | 750 " |
| Terramycin | Sterile water | 1000 " |

** On the basis of active constituent.
† By dilution from stock solution having a concentration of 1500 units per ml.
‡ Because of limited solubility in aqueous solution, it is advisable to affect solution of the crystals with several drops of 95% ethanol and then to dilute to volume with sterile buffer.

* The penicillin, streptomycin, aureomycin and chloramphenicol were supplied by Dr. Henry Welch, Antibiotics Division, Food and Drug Administration, Federal Security Agency. The terramycin was supplied by Dr. E. R. Weyer, Charles Pfizer & Co., Inc.

TABLE 2.—CRITERIA FOR INTERPRETATION OF SUSCEPTIBILITY

| *Antibiotic* | *Dosage Schedule* | *Av. Max. Blood Level Resulting from Indicated Dosage* | *Approx. Antibiotic Dose per Disc.* | *Relative Susceptibility when Inhibition Zone is Present* | *Relative Susceptibility when Inhibition Zone is Absent* |
|---|---|---|---|---|---|
| Penicillin | 300,000 units Procaine, daily/100,000 units crystalline q. 3 h. | 0.75–1.0 units per cc. | 1.0 unit | 1 unit or less S | > 1 unit R |
| Streptomycin | 0.5 gm. b.i.d. | 15 mcg. per cc. | 15 mcg. | 15 mcg. or less S | > 15 mcg. R |
| Chloramphenicol | 0.5 gm. q. 6 h. | 15 mcg. per cc. | 15 mcg. | 15 mcg. or less S | 15 mcg. R |
| Aureomycin | 0.5 gm. q. 6 h. | 4 mcg. per cc. | 4 mcg. | 4 mcg. or less S | > 4 mcg. R |
| Terramycin | 0.5 gm. q. 6 h. | 6 mcg. per cc. | 6 mcg. | 6 mcg. or less S | > 6 mcg. R |

S—Susceptible
R—Resistant

completely saturated. The disc is then gently deposited upon the agar surface. As many as 4 or 5 discs, each impregnated with a different antibiotic solution, may be placed on the surface of the inoculated plate*.

4. Plates are incubated overnight right side up at 37°C. and then examined for zones of growth inhibition around the discs.

5. An organism whose growth has been inhibited, regardless of the size of the growth-free zone, is reported as "susceptible". When no zone of inhibition is seen, the organism is considered as "resistant".

6. Our criteria for distinguishing between resistant and susceptible organisms are summarized for convenience in Table 2.

**Discussion.** To attempt to interpret results obtained with this procedure, it is necessary to consider the following: 1) a clear definition of the term "antibiotic susceptibility"; 2) an appreciation of the scope of the interpretation which can be placed upon *in vitro* sensitivity tests, 3) an understanding of the principles underlying agar diffusion tests.

An "antibiotic susceptibility" determination in the laboratory, either by a serial dilution test or an agar diffusion test, is actually the measuring of a finite antibiotic concentration, or range of concentrations, which is effective in producing some degree of growth inhibition of the test organism. This result is a numerical expression of little or no significance unless it is interpreted with regard to some reference standard. If the reference standard is the inhibiting concentration for a second organism, then it is possible to describe the susceptibility of the first in terms of the second. Thus we see that while the results of the tests for any 1 organism have a more or less absolute value, the interpretation of them in terms of susceptibility can only

* Positioning of the discs is facilitated by the use of a guide placed under the agar plate. Such a guide may be made from a sheet of white paper or cardboard which is inscribed with a circle. The circle has a diameter equal to that of the Petri dish bottom and is divided into five equal segments by means of radii. The loci upon which discs are to be deposited are indicated by means of 5 mm. diameter dots drawn on each radius at a distance of 25 mm. from the center of the circle. Well-separated discrete zones of growth inhibition, with diameters up to 25 mm., are thereby assured.

have a relative one. Consequently, antibiotic susceptibility is an expression of relative and not absolute values. If we are to speak of susceptibility, what is to be the reference standard? In our opinion, the clinical distinction between "resistant" and "susceptible" should be made with reference to the average maximum antibiotic concentration obtainable in blood of average patients, receiving the most commonly used dosage of the antibiotic. For example, a dosage schedule which produces blood concentrations below those which are necessary for inhibition as indicated by *in vitro* tests automatically labels the infecting organism as "resistant". However, if as a result of increased dosage or some other means, the blood levels are elevated beyond the *in vitro* inhibiting concentration, the same organism is now designated as "susceptible". For clinical purposes then, it is not necessary to know the finite concentration required for inhibition as long as it is less than the concentration attainable in blood with prescribed dosages. We are fully cognizant of the fact that the critical and effective concentration of an antibiotic is probably that which exists in the tissues at the actual site of infection rather than that which is present in the peripheral circulation. However, in view of the obvious difficulties in determining tissue concentrations and the rather universal agreement that blood concentrations correlate well with clinical response, the establishment of these blood level concentrations as a criterion is understandable. From the clinical standpoint, therefore, it is dosage and concomitant blood level concentration which govern the practical distinction between resistance and sensitivity. Hence, all that should be required of a susceptibility test is an observation of *in vitro* inhibition, regardless of degree, by an antibiotic concentration equivalent to the average maximum blood levels attainable with specified dosages.

One of us[2] has pointed out some of the difficulties encountered when an attempt is made to correlate results of susceptibility tests obtained in one laboratory with those in another. It was shown that these difficulties may be attributed to several factors, most important of which are: 1) non-uniformity of procedures used in different laboratories, 2) variation in criteria for growth inhibition, partial or complete.

Jackson and Finland[4] recently reported on a comparison of methods for determining sensitivity of bacteria to antibiotics *in vitro*. Defining sensitivity they refer to Heatley[3] and state that "the sensitivity of any given strain of organism to an antimicrobial agent is generally defined in terms of the concentration of the agent which inhibits the growth of the organism either partially or completely, or which kills the organisms within the time limit of the test". On the basis of this definition, upon which their entire investigation is centered, they conclude: 1) that the minimum inhibiting concentration of any one antibiotic for a given organism shows wide variations depending upon the method used; 2) that certain methods yield values which fall within a narrower range than that indicated by others; 3) that all susceptibility tests should be used as a *qualitative guide and interpreted solely on the basis of distinguishing between susceptible and resistant organisms.*

The final conclusion, with which we are in complete accord, unquestionably points up our thesis that susceptibility is a relative and not an absolute value and that it is fallacious to insist on quantitatively definitive values of inhibiting concentrations when the need is not indicated.

Having established our criterion of relative susceptibility, it is necessary

to determine whether our method adequately distinguishes between resistance and sensitivity. When a plate prepared in the described manner is placed in an incubator, two processes occur simultaneously: 1) Organisms begin to grow and increase in number. 2) Antibiotic diffuses in all directions from the paper disc through the agar so that a concentration gradient is established, concentration being highest at the periphery of the disc and progressively diminishing as the distance from this point increases. Within this area, organisms are exposed to a continuous gradation of antibiotic concentrations so that at some point there exists a concentration of antibiotic which is non-inhibitory for the organism and it will grow freely. The area within which growth is suppressed is the zone of inhibition and with *certain limitations* its diameter is a measure of the relative susceptibility of the organism.

The limitations become apparent with the realization that: 1) The concentration of antibiotic at any given point is constantly changing during the incubation period. 2) The duration of the lag phase of the organism and the rate of diffusion of the antibiotic will determine whether macroscopic growth does or does not occur at a particular point. Thus, for a single antibiotic, organism A, which has a longer lag phase than organism B, will appear to be more sensitive. 3) The diameter of the zone of inhibition depends upon the absolute quantity of antibiotic absorbed on the disc.

Precise statements of the magnitude of the inhibiting concentration which corresponds to any given zone diameter cannot be made unless these factors are known and controlled. However, if a zone of inhibition appears around a disc containing a known amount of antibiotic and this amount corresponds to the average maximum blood level attainable with specified dosages, it can then be said that the organism is susceptible to this amount of antibiotic or less. Under the same conditions an organism is considered resistant if there is no zone of inhibition.

**Summary and Conclusions.** 1. A simple, rapid, standardized laboratory procedure for determination of bacterial susceptibility to antibiotics is described. The procedure is the result of experience gained from several thousand evaluations which have been made with satisfactory results to the clinician, the patient, and the laboratory.

2. The primary criterion for distinguishing between resistant and susceptible organisms is the presence or absence of zones of inhibition, regardless of diameter, surrounding filter paper discs containing a specific quantity of antibiotic. The amount of each antibiotic placed on a disc corresponds to the average maximum blood level concentrations attainable in average patients receiving definite prescribed dosages.

3. Emphasis is placed on the unimportance (from the clinician's standpoint) of quantitative values of inhibiting concentration of antibiotic when defining relative susceptibility.

4. It is suggested that all susceptibility tests, serial dilution, and agar diffusion, be used solely as a qualitative guide to distinguish between susceptible and resistant organisms.

ACKNOWLEDGEMENTS. The writers wish to express their appreciation for the technical assistance rendered by the staff of the Division of Bacteriology and Serology, Pathology Laboratories, Philadelphia General Hospital, and for the data on blood level concentrations made available to them by Dr. N. H. Schimmel, Technical Director of the Chemotherapy Laboratory, Hospital of the University of Pennsylvania,, Philadelphia, Pennsylvania.

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# COMPARISON OF A NEW STEP TEST WITH A TREADMILL TEST FOR THE EVALUATION OF CARDIORESPIRATORY WORKING CAPACITY*

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An adequate history is often sufficient to evaluate the approximate functional working capacity of patients with cardiovascular or pulmonary diseases. Although the physiological differences between normal and abnormal capacity are only quantitative, there has been no suitable method that was generally available for determining such differences over the entire range. Numerous attempts have been made to establish various types of performance tests, as well as to evaluate critically many of the physiological measurements pertaining to functional capacity. Excellent reviews have been written by Simonson and Enzer[7], and more recently by Wahlund[8]. A different approach has been suggested by Bruce *et al.*[4] This was based upon a study of the normal pathways of respiratory and circulatory adaptation to exercise of moderate severity[3] and a statistical analysis of the inherent variability of the several parameters.[5] An index of physical fitness was formulated as an integrated ratio of three fundamental aspects of performance which proved to have low coefficients of variability.[4] These characteristics were the duration of exertion, efficiency of oxygen uptake, and the rapidity of circulatory recovery. This index was found to vary inversely with the magnitude of the pressure gradient for oxygen between functional alveolar air and arterial blood[4]. Since it also varied directly with the oxygen saturation of the arterial blood, physical performance, when properly motivated, appeared to be dependent upon the availability of oxygen to the tissues.

* This study was supported in part by Grant-in-aid H-908(R) from the National Heart Institute.

TABLE 1.—PHYSICAL CHARACTERISTICS, DIAGNOSES AND SEQUENCE OF TESTS IN NORMALS AND PATIENTS

*Normals (Group A)*

| *No.* | *Initial* | *Age* | *Sex* | *Ht.* | *Wt.* | *% Deviation from Standard* | *Test 1st* |
|---|---|---|---|---|---|---|---|
| 1. | P. S. | 22 | F | 66 | 125 | −6.4 | TM |
| 2. | H. K. | 32 | F | 65 | 163 | +17.8 | TM |
| 3. | F. S. | 42 | F | 61.75 | 138 | +4.4 | TM |
| 4. | J. H. | 26 | F | 69 | 156 | +5.8 | TM |
| 5. | C. J. | 46 | F | 63.75 | 130 | −8.5 | TM |
| 6. | M. N. | 33 | F | 64 | 152 | +13.5 | TM |
| 7. | M. D. | 33 | F | 64 | 125 | −4.8 | TM |
| 8. | E. J. | 49 | F | 65 | 190 | +23.7 | ST |
| 9. | J. D. | 24 | F | 64 | 160 | +21.3 | ST |
| 10. | L. O. | 29 | F | 66 | 143 | +5.6 | ST |
| 11. | H. D. | 28 | M | 76.5 | 210 | +7.6 | TM |
| 12. | T. T. | 36 | M | 73 | 195 | +6.7 | TM |
| 13. | G. W. | 29 | M | 71 | 180 | +8.9 | TM |
| 14. | H. M. | 29 | M | 72 | 198 | +15.2 | TM |
| 15. | J. H. | 40 | M | 67 | 135 | −13.4 | TM |
| 16. | H. K. | 32 | M | 71.5 | 155 | −7.1 | ST |
| 17. | H. L. | 39 | M | 70 | 175 | +5.7 | ST |
| 18. | B. B. | 23 | M | 68.5 | 140 | −10.7 | ST |
| 19. | O. S. | 34 | M | 69.75 | 160 | −1.2 | ST |
| 20. | D. C. | 30 | M | 74.5 | 185 | +5.4 | ST |

*Abnormals (Group B)*

| *No.* | *Initial* | *Age* | *Sex* | *Ht.* | *Wt.* | *% Deviation from Standard* | *Test 1st* | *Diagnosis* |
|---|---|---|---|---|---|---|---|---|
| 1. | B. B. | 40 | M | 65.5 | 149 | +2.7 | TM | RHD, MI and MS |
| 2. | D. M. | 45 | M | 68 | 130 | −23.1 | ST | HCVD |
| 3. | F. B. | 60 | M | 70 | 140 | −23.6 | TM | ASHD |
| 4. | G. L. | 62 | M | 62 | 136 | −2.2 | ST | ASHD, Myxedema |
| 5. | M. D. | 63 | M | 71 | 181 | +1.6 | TM | Chronic Lymphatic Leukemia |
| 6. | J. M. | 50 | M | 67 | 137 | −13.9 | TM | Post-op RUL lobectomy |
| 7. | C. M. | 62 | M | 69 | 154 | −9.1 | ST | HCVD |
| 8. | E. R. | 33 | M | 65 | 116.5 | −20.2 | TM | Post-op Pericardiectomy |
| 9. | J. C. | 41 | M | 67 | 137 | −11.7 | ST | Cardiomegaly Etiology undetermined |
| 10. | M. M. | 39 | F | 58 | 83 | −43.4 | TM | Pulmonary Fibrosis Bronchiectasis |
| 11. | M. S. | 36 | F | 61.5 | 150 | +16.7 | ST | HCVD |
| 12. | L. L. | 35 | F | 61 | 129 | +3.1 | ST | HVD Post Partum Toxemia |
| 13. | A. H. | 77 | F | 61.5 | 109 | −23.9 | ST | ASHD |
| 14. | L. G. | 65 | F | 57 | 106 | −21.7 | ST | ASHD, Asthma |
| 15. | D. M. | 43 | F | 60 | 125 | −1.6 | ST | HVD |
| 16. | E. S. | 29 | F | 63 | 136 | +8.8 | ST | RHD, MS and MI |
| 17. | J. C. | 64 | M | 70 | 125 | −38.4 | ST | ASHD |
| 18. | J. C. | 18 | M | 71.5 | 120 | −32.5 | TM | CHD (Eisenmenger's) |
| 19. | R. G. | 13 | M | 71 | 116 | −18.1 | ST | Funnel Chest (Severe) |
| 20. | R. G. | 44 | F | 59 | 159 | +21.4 | TM | RHD, MS, MI, AI, & AS |

TM—Treadmill Test
ST—Step Test
RHD—Rheumatic Heart Disease
MI and MS—Mitral Insufficiency and Mitral Stenosis
AI and AS—Aortic Insufficiency and Stenosis
HCVD—Hypertensive Cardiovascular Disease
ASHD—Arteriosclerotic Heart Disease
RUL—Right upper lobe
CHD—Congenital Heart Disease

Because of the requirements for special equipment,[4] this testing procedure has not been generally available. Since then attempts have been made to simplify the procedure, with reference to both equipment and measurements, in order to make it available to interested physicians. It is the purpose of this report to describe a step test employing the same principles as the treadmill test, and to compare the results obtained with those of the treadmill procedure on the same persons.

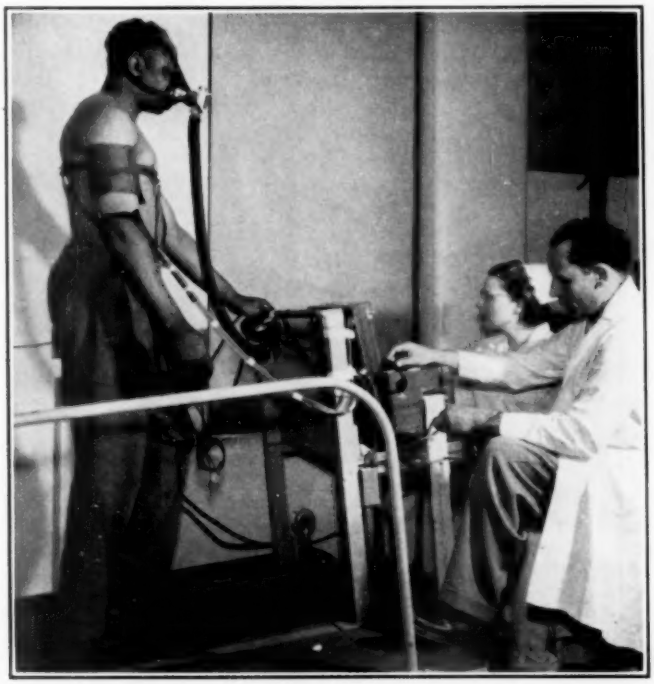

FIG. 1.—Illustration of the treadmill technique for performing the exercise tolerance test. The patient is walking on a 10% grade at 1.7 mph. Note the face mask with attached inspiratory and expiratory valves, expired air mixing tube, sphygmomanometer cuff on the arm, and chest electrodes held in place with a rubber strap.

**Methods.** Forty subjects were studied in the resting (non-basal) state: 20 were normal subjects, ranging in age from 22 to 49 years, and 20 were patients from 13 to 77 years of age with various types of cardiorespiratory disease. The physical characteristics and diagnoses are shown in Table 1. Each individual was instructed how to perform the tests, and then was equipped with chest-lead electrodes, face mask and sphygmomanometer cuff as illustrated (Fig. 1 and 2). Some performed the treadmill test first, others the step test, as indicated in Table 1. There was sufficient time allowed between the tests to assure complete recovery. The treadmill test was performed, as described previously[4], with the subjects walking slowly on a 10% grade at the rate of 1.7 mph for 10 minutes, or less, if 10 minutes exceeded the limits of subjective tolerance. A comparable work-load, requiring a 3- to 4-fold increase in oxygen consumption over the resting level, was chosen for the step test.

The step test procedure required a single step-up and return to the floor level at the rate of 20 steps per minute. The subjects were watched closely and advised to per-

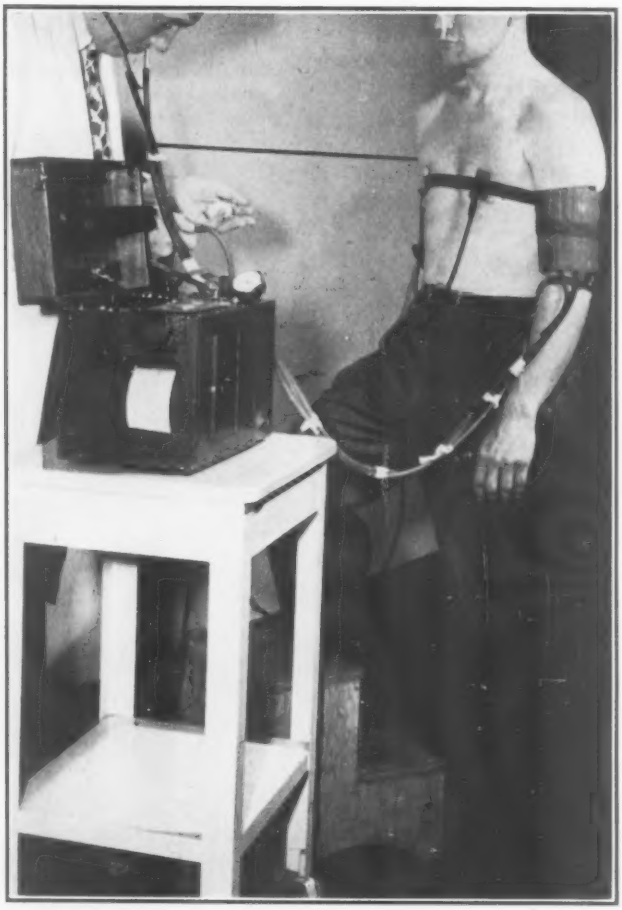

FIG. 2.—Illustration of the simplified step test technique. The patient steps up on a single 9-inch step 20 times per minute. The blood pressure and electrocardiogram are obtained as before. The respiratory rate is counted by watching the movements of the paper indicator attached to the nose.

form this test either more or less rapidly as indicated in order to establish and maintain this rate of working. The step was 9 inches high. The duration of work was limited arbitrarily to 10 minutes or less, as determined by the patient's tolerance for exertion. (See outline of step test procedure.)

Continuous observations were made of the respiratory rate, expired air oxygen tension (Pauling meter) heart rate (electrocardiogram) and blood pressure, at 1-minute intervals throughout the 4 minutes of rest (patient sitting in a chair), 1 minute of standing, 10 minutes of exercise, and 5 minutes of recovery. The mean respiratory efficiency during exercise was derived in 2 stages as follows:

a) Oxygen concentration of expired air equaled average expired air $pO_2$ during exercise x 100 Barometric pressure—vapor pressure at room temperature;
b) Respiratory efficiency, in volumes per 100 cc., equaled 20.9—oxygen concentration of expired air.

The average respiratory efficiency has been compared with 100 times the reciprocal of the average respiratory rate during the same period of exercise for all tests.

For the *treadmill test*, the physical fitness index[4] equaled:

duration of exercise x average respiratory efficiency during exercise x 100, divided by the total heart beats for first three minutes of recovery.

Normal indices range from 13 to 26. The exercise was limited arbitrarily to 10 minutes with either the treadmill or the step test. For the *step test* the physical fitness index equaled:

duration of exercise x number of steps taken* x 10,000, divided by the average exercise respiratory rate x total heart beats for 3 minutes of recovery x prescribed number of steps at the rate of 20 per minute.

The electrocardiographic changes in the precordial lead $CB_4$ were evaluated according to the same criteria described by Yu *et al.*[2], using the same arrangements of electrodes on the chest.

### Outline of Step Test Procedure

*Requirements*:

1. Ambulatory patients willing to perform the test
2. A single step, 9 inches high
3. Watch with second hand, preferably a stop-watch
4. Direct-writing electrocardiograph
5. Sphygmomanometer and stethoscope
6. Mechanical hand counter for counting steps**
7. Observer(s)

*Procedure*:

1. Instruct the patient to step up and down at the rate of 20 steps per minute (complete cycle in 3 seconds)
2. Attach:
   a) paper indicator to nose for respiratory rate (Fig. 2)
   b) chest belt and electrodes (recording on lead I)
      (1) indifferent, right scapula, RA cable
      (2) ground, anterior right chest, RL cable
      (3) localizing, corresponding to V4 position, near normal point of maximum impulse, LA cable
   c) blood pressure cuff on arm
3. Observations:
   a) at one-minute intervals (rest, exercise, and recovery)
      (1) respiratory rate
      (2) heart rate (electrocardiogram)
      (3) blood pressure
      (4) number of steps performed
   b) duration of exertion
4. Duration of observations:
   a) rest, sitting in chair 4 minutes; standing, 1 minute
   b) exercise, 10 minutes
   c) recovery, 5 minutes

*Data Needed for the Physical Fitness Index*:

1. Duration of exertion
2. Average respiratory rate during exercise
3. Total heart beats for first 3 minutes of recovery
4. Total number of steps taken

*Formula for Physical Fitness Index*:

duration of exercise x number of steps taken x 10,000, divided by the average exercise respiratory rate x total heart beats x prescribed number respiratory rate x for 3 minutes of x of steps at the recovery rate of 20 per minute.

*Normal Range of Physical Fitness Scores*:

9 to 19, average 14. Range of scores in patients with varying degrees of disability from cardiovascular and pulmonary diseases: <1 to 23.

*Significance of Physical Fitness Index*: See discussion in text.

**Results.** 1. Comparison of Step Test with Treadmill Test. The physiological responses of both normal subjects and patients with various cardiorespiratory diseases are presented in Table 2. The data obtained from the step test are compared with those from the treadmill test. Regardless of which procedure was first, in nearly all instances the step test was considered subjectively a harder task. This may have been due to the form of exercise

* This correction was necessary because many individuals found it impossible to perform the test exactly with the regularity achieved by walking on the treadmill.

** In many instances this may be done by the patient.

as well as differences in intensity of work-load. Despite the identical duration of exertion in all normals, the heart rate, systolic blood pressure, and QT/TQ ratio during exercise as well as the 3-minute recovery heart rate tended to be slightly higher with the step test than with the treadmill test. The respiratory efficiency, and 100 times the reciprocal of the respiratory rate during exercise, were similar. Because of the differences in circulatory performance, the physical fitness index (calculated either from the respiratory efficiency or the respiratory rate) tended to be somewhat lower for the step test. Although there were greater variations in the patients studied, due to wide differences in functional capacity, the comparative results with the two forms of exercise were similar to those observed for the normal subjects. In addition, the duration of exercise was slightly less for the step test than for the treadmill test in this patient group.†

TABLE 2.—COMPARATIVE RESPONSES OF NORMALS AND PATIENTS TO STEP-TEST AND TREADMILL EXERCISE

| | *30 Normals* | | | | *20 Patients* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Treadmill* | | *Step Test* | | *Treadmill* | | *Step Test* | |
| | *Average* | *(Range)* | *Average* | *(Range)* | *Average* | *(Range)* | *Average* | *(Range)* |
| *Exercise:* | | | | | | | | |
| Duration, minutes | 10 | (10) | 10 | (10) | 8.5 | (2–10) | 7.9 | (1.5–10) |
| Heart Rate/minute | 123 | (94–137) | 132 | (110–151) | 123 | (96–157) | 132 | (99–149) |
| Blood Pressure, mmHg | 156/83 | (128–187/71–101) | 161/84 | (136–199/72–100) | 158/91 | (118–219/53–129) | 170/95 | (110–230/56–128) |
| Respiratory Efficiency Vol. % | 5.0 | (4.1–5.9) | 5.0 | (4.2–6.8) | 3.8 | (2.2–5.5) | 3.9 | (2.1–6.3) |
| 100/Respiratory Rate | 4.5 | (3.3–5.8) | 4.5 | (3.2–6.3) | 3.5 | (2.1–5.2) | 3.5 | (2.4–4.8) |
| QT/TQ Ratio | 1.4 | (1.0–1.9) | 1.5 | (1.0–2.2) | 1.5 | (.9–2.8) | 1.7 | (.9–2.8) |
| QTc | 0.4 | (.33–.46) | 0.4 | (.33–.44) | 0.4 | (.33–.46) | 0.4 | (.37–.50) |
| *Recovery:* | | | | | | | | |
| 3 Minute Heart Rate | 290 | (220–366) | 327 | (228–411) | 313 | (228–403) | 333 | (234–433) |
| Physical Fitness Index (Calculated from R.E.) | 17.2 | (13.4–22.3) | 15.8 | (11.9–21.4) | 11.1 | (.8–19.1) | 8.9 | (1.6–17.7) |
| Physical Fitness Index (from 100/R.R.) | 15.8 | (11.0–21.6) | 14.2 | (9.4–19.2) | 10.1 | (.8–23.0) | 7.9 | (1.5–16.4) |

2. Validity of the Physical Fitness Index Calculated from the Respiratory Rate During the Step Test. In simplifying the treadmill technique for studying exercise tolerance, two changes have been made. First, a step test was substituted for the treadmill stress of exercise. Secondly, 100 times the reciprocal of the respiratory rate was substituted for the respiratory efficiency. The latter was the mean difference, in volumes per 100 cc., between inspired and expired air as determined by a Pauling oxygen analyzer. Fig. 3 shows the relationship of the respiratory efficiency to 100 times the reciprocal of the respiratory rate, in all subjects, during both forms of exercise. Whereas the coefficient of correlation was $+0.666 \pm .124$ ($P < .074\%$) for the patients, it was only $+0.329 \pm$

† An occasional patient, not included here, was able to walk on the treadmill, but unable to perform the step test because of poor coordination, or arthritis.

.199 ($P>28.0\%$) for the normal subjects. This reflected the fact that normal subjects show little variation in respiratory rate at moderate work loads. Patients with cardiac or pulmonary diseases, especially if decompensated, show considerable changes in breathing rates with exertion. Fig. 4 shows the almost linear relationship between the corresponding physical fitness scores calculated from the separate formulae for the two different forms of exercise. The coefficients of correlation between these scores were $+0.666 \pm .124$ ($P<.074\%$) and $+0.760 \pm .094$ ($P<.001\%$) for the normal subjects and patients, respectively. Two patients, E.S. and R.G., had much lower $P.F.I._{RR}$ scores. Each walked for 10 minutes on the treadmill, but was unable to continue the step test for more than 6 minutes. Other less striking differences between the fitness scores for the two procedures were due to minor variations in endurance, respiratory performance, or recovery heart rate. The chief reason for the lower average physical fitness score with the step test was the higher average heart rate in recovery.

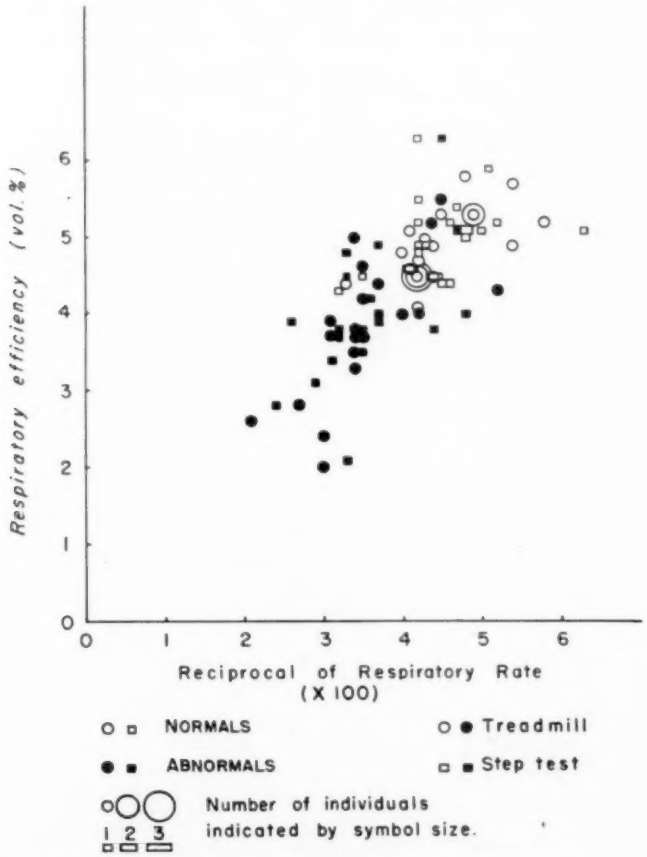


FIG. 3.—Relationship of the mean exercise respiratory efficiency to 100 times the reciprocal of the mean exercise respiratory rate in 40 individuals during both the step test and the treadmill test.

3. Effects of Age, Sex, and Weight on Physical Fitness. Previous studies indicated a slight decrease of .04 volumes per 100 cc. per year in average exercise respiratory efficiency during treadmill walking in normal subjects between the ages of 25 and 50 years[1]. There was no apparent relationship of age to the other variables, and none with either sex or body weight. As indicated in Fig. 5, the present data suggest a slight but different relationship than that noted earlier. With either form of exercise, normals show higher respiratory efficiency between the ages of 22 and 36 years. There were too few older individuals to evaluate this relationship adequately. In accord with Wahlund's observations[8], many of the patients with impaired fitness were underweight (Fig. 6). Much larger numbers of individuals would be required to establish this trend with certainty, however.

4. Electrocardiographic Responses to exercise. The ranges of sinus tachycardia observed during exercise with the step test are shown in Table 2. All but one normal had higher rates on the step test than the treadmill. None developed an arrhythmia or paroxysmal tachycardia as a result of the stress. The P waves were frequently notched, probably because of the electrode positions that were used. None developed either an AV heart block or an interventricular conduction defect. Respiratory variation in voltage of QRS and T waves as well as minor displacement (less than 1 mm.) of the RS-T segment were more common with the step test than with the treadmill test. In the normal subjects, premature ventricular contractions never occurred.

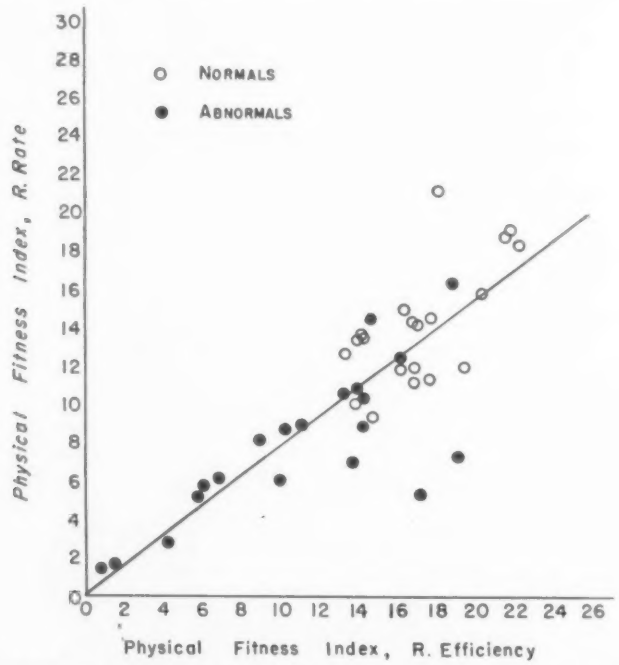


Fig. 4.—Relationship of the physical fitness index during the step test (calculated from the respiratory rate) and the physical fitness index during the treadmill test (calculated from the respiratory efficiency) in 40 individuals.

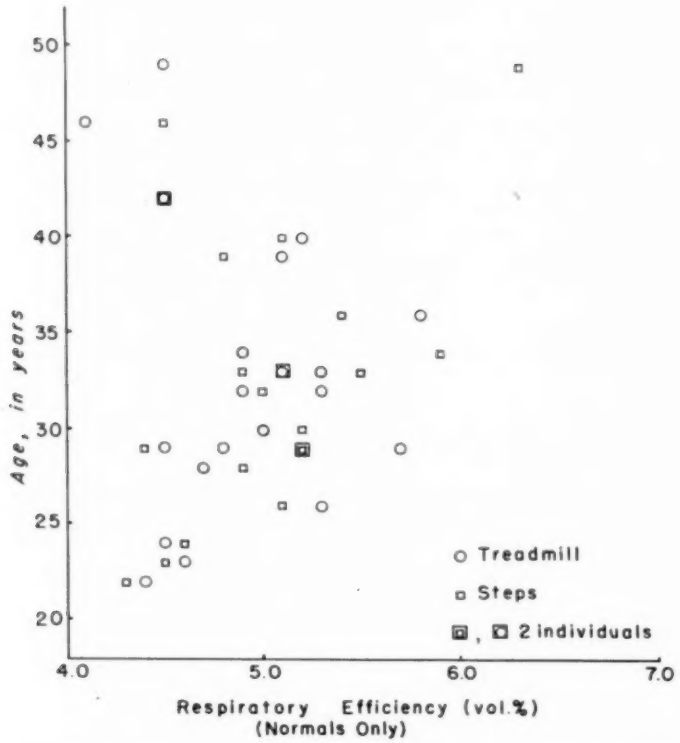


FIG. 5.—Variations in mean exercise respiratory efficiency with age in normal subjects.

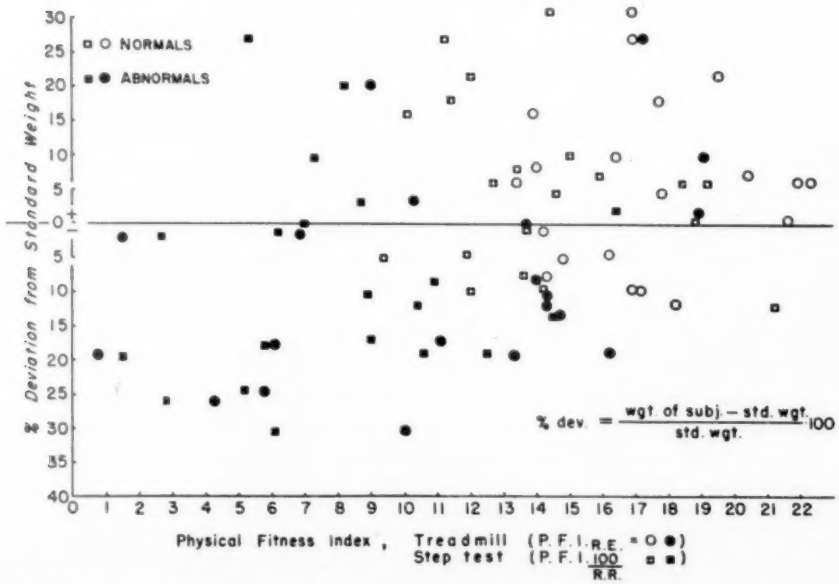


FIG. 6.—Relationship of percentage deviation from ideal weight (for age, sex and height) to the physical fitness indices.

and the T waves were always upright, although the voltage diminished in a few. During recovery from the step test, 8 of the 20 showed an appreciable increase in the height of the T wave. About half of the normals failed to show the expected increase in $QT_c$[9] during the step test. Two had very low QT/TQ ratios, and 4 had values exceeding 2.2 during exertion.

Fifteen of the patients had faster heart rates with the step test than on the treadmill. Five exhibited premature ventricular contractions, usually during the second and third minutes of exercise, when the maximum respiratory efficiency occurred. Half of the patients showed RST depression of more than 0.5 mm. with every beat; 3 were taking digitalis at the time. Six had higher T waves during exertion than at rest, and 5 developed higher T waves in recovery. About half of the patients showed diminished $QT_c$ values and QT/TQ ratios over 2.2 during exertion. Altogether, there was a slightly higher incidence of abnormalities in the patients during the step test than during the treadmill test.

**Discussion.** Three major components of physical fitness have been described. First there is static fitness or soundness of physical structure and function together with freedom from disease. This is appraised by clinical examination of patients. Secondly, there is dynamic fitness, or the psychophysiologic ability to do work. The physical fitness indices under discussion represent the integrated ratio of psychosomatic factors in endurance as well as the function of the respiratory and circulatory systems in relation to standardized exertion[4]. Thirdly, there are specialized skills that require neuromuscular training for specific tasks. Obviously a suitable testing procedure should employ skills that are common to the largest number of subjects to be tested. Furthermore, performance of the test should not unduly tax a patient's motivation and physical capacity and yet should involve large muscle groups. From the data reported herein, it is apparent that 10% grade-walking at a slow pace of 1.7 mph for 10 minutes is subjectively easier, and functionally slightly less strenuous than stepping up and down a 9-inch step 20 times per minute for 10 minutes. It is important to note, however, that the exact form of exercise is not particularly critical as long as the requirements stated above are met. Other studies have shown that the same range of physical fitness scores may be obtained from normal subjects performing a comparable amount of work on a bicycle ergometer[2].

Both the implications and the limitations of physical fitness testing have been discussed previously[4]. It is important to emphasize, however, that a subnormal score does not necessarily indicate the presence of disease; nor does a high score exclude the possibility of disease. A patient may have impaired static fitness, yet be well compensated, and have a capacity for moderate work within the normal range. Another patient, contrariwise, may have impaired dynamic fitness despite unimpaired static fitness, because of inappropriate motivation to perform, or undue anxiety about the nature of his performance. Despite these limitations, the testing of physical fitness has been informative, and now that it can be simplified, it may become more useful. But the clinical interpretation of the significance of a patient's physical fitness will always require careful clinical judgment based upon knowledge of history, physical, and laboratory findings.

There are two additional limitations of the step test method that were not apparent with the treadmill procedure.

It is technically more difficult for the work load to be standardized in proportion to the patient's weight. The irregularity which may occur in the rate of stepping can be corrected by taking the number of steps performed into consideration in the final score. Secondly, the respiratory rate is more variable than the respiratory efficiency, and, in normals at least, does not exhibit a marked change with moderate exertion. Nevertheless there is a sufficient relationship between the exercise respiratory efficiency and 100 times the reciprocal of the respiratory rate to substitute the latter measurement in the formula for estimating the physical fitness index. Using these methods, the normal range of physical fitness by the step test varies from 9 to 19, with an average of 14.

**Summary.** 1. The exercise performance of 20 normal subjects and 20 patients with various cardiorespiratory diseases has been evaluated by means of a new step test in comparison with a previously described treadmill procedure.

2. The principles of the treadmill test can be applied to the step test in estimating the index of physical fitness.

3. The respiratory rate may be substituted for the respiratory efficiency in estimating physical fitness.

4. The limitations of the new step test are discussed.

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# STUDY OF THE MERCURIAL DIURETIC, THIOMERIN (MERCAPTOMERIN), BY SUBCUTANEOUS INJECTION IN PATIENTS WITH CONGESTIVE FAILURE, WITH SPECIAL REFERENCE TO LOCAL REACTIONS

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During the past few years, several reports have appeared on experimental and clinical studies of a new diuretic agent under the name of thiomerin‡. The material is chemically identical with mercuzanthin (mercurophylline) except for the fact that theophylline is replaced by sodium mercapto-acetate, resulting in a compound more resistant to dissociation. The reports indicate that this compound represents the development of an organic mercurial with potent diuretic action, low toxicity, and negligible irritant action at the site of the subcutaneous injection.

In a recent study on the management of congestive failure[10], we called attention to the fact that the need for a physician to make the injection of the mercurial diuretic by the intramuscular or intravenous route is an obstacle to the general application of the most effective method of treatment, and that for the most successful control of congestive failure it is necessary that the patient or a member of the family acquire the technique of injection. It was noted that the problem of controlling congestive failure is analogous to that of diabetes, in the treatment

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** Work done during the tenure of a New York Heart Association Fellowship.
‡ Mercaptomerin is recognized as the generic name and Thiomerin Sodium as the protected name by the Council on Pharmacy and Chemistry[7].

of which it is likely that progress would have been greatly retarded had it proved necessary to have a physician for every dose of insulin. Patients master the technique of a subcutaneous injection more readily than that of the intramuscular injection. Therefore, the possibility of a non-irritant organic mercurial which may be administered subcutaneously suggested a discovery of outstanding importance.

**Observations.** DAILY DOSE OF THIOMERIN. Thiomerin was made available to us by Campbell Products, Inc., in order to enable us to secure some first-hand experience with its efficacy as a diuretic. Fig. 1 shows an example of the use of thiomerin by the intensive method of treatment of congestive failure in which a daily dose of the mercurial is given. The response was essentially similar to that described in an extensive study of congestive failure in which mercuhydrin (meralluride) was employed as the diuretic agent[10] and given chiefly by the intramuscular route.

DIURETIC BIOASSAY OF THIOMERIN. We have developed a method for the bioassay of diuretic agents in ambulant patients with congestive failure[11]. It is based on the dosage-response curve and takes into account the current principles employed in laboratory assays. The measure is the loss of weight 24 hours after the injection in each patient. This method was applied to 17 patients with congestive failure. There were 3 dose levels, namely, 1.0, 1.4, and 2.0 cc., and the thiomerin subcutaneously was compared with mercuhydrin intramuscularly (taken as the standard) in each patient. The mercuhydrin used was the solution from the 10 cc. vials supplied by the Lakeside Laboratories (Control No. 0551). The thiomerin was a market specimen (Lot No. 5103), and was injected within 1 hour of the time the solution was made. An analysis of variance and calculation of potency[11] showed that the 2 materials had the same qualitative action, and that the potency ratio for the solutions of mer-

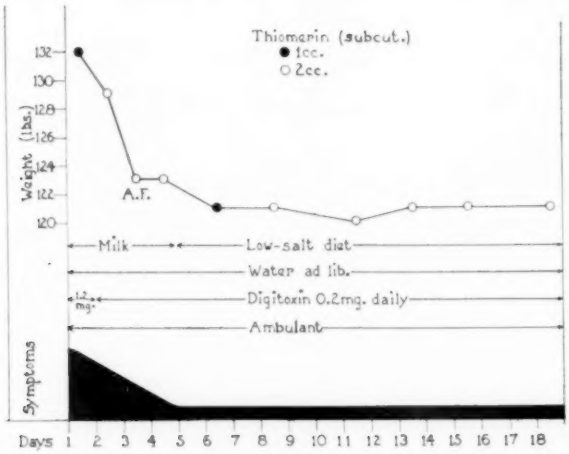


FIG. 1.—Typical response of advanced congestive failure to intensive treatment with thiomerin injected subcutaneously in 73-year old female with arteriosclerosis, essential hypertension, auricular flutter, and advanced failure. Symptoms were dyspnea, orthopnea, cyanosis, enlarged liver, edema, and weakness.

cuhydrin and thiomerin of commerce was 1:1.26. The confidence limits at P 0.05 were from 0.96 to 1.65. When the 2 materials were compared in terms of the weight of the compounds, the potency ratio for mercuhydrin and thiomerin was 1:1.10 with confidence limits at P 0.05 from 0.84 to 1.45. We may, therefore, conclude that the diuretic potency of the conventional solution of thiomerin by subcutaneous injection is not substantially different from that of mercuhydrin.

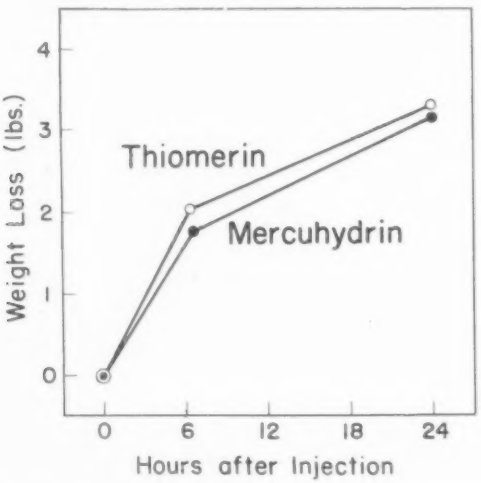


FIG. 2.—Comparison of rate of diuretic action of thiomerin and mercuhydrin, both by subcutaneous injection. Each of 17 patients with congestive failure received 2 cc. of thiomerin and on another occasion 2 cc. of mercuhydrin. The average loss of weight 6 hours and again 24 hours later is charted for each preparation.

CURVE OF DIURETIC ACTION OF THIOMERIN. It has been stated by several observers that the diuresis after thiomerin develops more slowly and lasts longer than that after other mercurial diuretics in common use, although Vander Veer *et al.*[24] found the curve of action (onset, peak, duration) for thiomerin similar to that for mercuzanthin. We tested this point by comparing the weight loss after 6 hours and again after 24 hours in the case of thiomerin and mercuhydrin, both given subcutaneously. The results (Fig. 2) show that the speed of development of the diuretic action is not conspicuously different for the 2 compounds by subcutaneous administration.

REACTIONS TO THIOMERIN. The more important question which concerned us was that of local or systemic reactions to this material, and especially to the subcutaneous injection, for while there is the indication from animal experiments that thiomerin, when tested in a particular fashion, discloses low toxicity as an organic mercurial, none of the preparations in common use, such as mercuhydrin, salyrgan-theophylline (mersalyl and theophylline), or mercuzanthin, exerts sufficient toxicity in the usual doses employed by intramuscular injection to constitute a problem[10]. The most significant contribution by such a preparation lay in the possibility that it might be generally available for injection by the subcutaneous route. In the preliminary observations, we noted that in some pa-

tients the subcutaneous injection of thiomerin into the arm or thigh was barely perceived by the patient, and, as noted by others, produced no more discomfort than a similar injection of physiological salt solution. However, in some patients fairly severe reactions appeared at the site of injection. As our experience enlarged, more unpleasant local reactions appeared than we had been led to expect from reports brought to our attention. Accordingly, it was deemed desirable to make a more extended study of this problem.

The observations reported here relate to 676 injections of thiomerin in 209 patients, although since the study was terminated, we have had much more experience, with some of the more recent lots of commerce, and with substantially similar results.

Most of the patients were in regular attendance at the cardiac clinics and some of them were at one time or another admitted to the hospital for the treatment of congestive failure. The common etiologic varieties of heart disease, namely, rheumatic, arteriosclerotic, and hypertensive, were represented. The ages ranged from 28 to 74. Sixty per cent of them were females. The vast majority had been under prolonged treatment with one or another organic mercurial diuretic. Some received mercuzanthin, others salyrgan-theophylline, but most of them were under treatment with mercuhydrin at the time they were diverted to the study of thiomerin.

Four lots of thiomerin were used: No. 248, No. 348, No. 548, and No. 029. The solutions were prepared with the ampules of sterile water then supplied with the vials of the drug. The solutions were colorless, clear, and free of visible particles at the time of injection.

This portion of the investigation was carried out in 3 phases, and it may be advantageous to examine the results in this way. The first involved a group of 43 patients of better than average intelligence for the clinic population. They were informed of the nature of the new material, of its possible advantages, and of the chance of an occasional reaction, for the purpose of securing their cooperation in continuing treatment even after a reaction. We thought this might help obtain the maximum amount of information concerning the behavior of the new drug. Members of this group sometimes entered the hospital for more intensive treatment. For about half of these patients, this was the first experience with mercurial diuretics, the remainder having been under treatment with mercuhydrin by intramuscular injection. The incidence of troublesome local reactions to the intramuscular mercuhydrin was negligible. Our general experience with mercuhydrin in the matter of pain at the site of injection into the biceps and gluteal muscles was described in a previous study[19]. In the majority of cases there was either no pain or barely perceptible discomfort. It was the rare case in which severe pain resulted. The study in this group was carried out during the latter half of 1948. Two specimens of thiomerin, No. 248 and No. 348, were used in these patients. A 10-cc. solution was made up, and it was stored in the refrigerator after each injection. In some instances, the dose was that of a freshly prepared solution, but the age of the solution varied. Only 18 of the 457 injections (4%) were made with solutions older than 10 days, but all of these were colorless and free of turbidity. A small hypodermic needle, usually of 24 or 26 gauge and ⅝ inch long, was used. It was plunged in at an angle to insure subcutaneous and not intramuscular injection. The sites were the arms, the thighs, or the buttocks. The authors made the injections.

The data concerning the 43 patients are summarized in Table 1. It may be noted that a reaction occurred in nearly half of the patients. Nearly one-third of the doses gave rise to a reaction in the form of substantial pain, inflammation, ecchymosis, or fibrous nodule. One patient developed 3 areas of slough on the thighs, leaving deep craters which took months to heal. Seven doses in 3 patients gave rise to general malaise, muscular aches, chills, and fever, characteristic of an allergic reaction.

In order to see the relation between the reactions and the dosage regimen in better perspective, all 43 case records were charted. Samples of the various types are reproduced in Figs. 3 and 4. Case 1 shows the type with a relatively long interval between doses and only an occasional reaction, the

TABLE 1.—REACTIONS TO SUBCUTANEOUS INJECTION OF THIOMERIN IN 43 PATIENTS ON A PROTRACTED COURSE OF TREATMENT

| | |
|---|---|
| Total number of patients | 43 |
| Males | 18 |
| Females | 25 |
| Total number of injections | 457 |
| Average number of injections per patient | 11 |
| Number of doses of thiomerin | |
| 0.25 and 0.5 cc | 3 |
| 1.0 cc | 194 |
| 1.5 cc | 29 |
| 2.0 cc | 231 |
| Number of doses with lot No. 248 | 202 |
| Number of doses with lot No. 348 | 255 |
| Patients and injections with reaction | |
| Number of patients | 19 (44% of all patients) |
| Number of injections received by these patients | 283 (62% of all injections in the 43 patients) |
| Number of injections which caused reactions | 123 (27% of all injections in the 43 patients) |

| Types of reactions and incidence related to all 43 patients | *Patients* % | *Injections* % |
|---|---|---|
| Pain | 28 | 13 |
| Inflammation | 12 | 4 |
| Nodule | 33 | 22 |
| Ecchymosis | 2 | 0.2 |
| Slough | 2 | 0.6 |
| General systemic | 7 | 1.5 |

first occurring after the fourth dose. Cases 2, 3, and 4 show more intensive dosage plans, reactions appearing with the first dose, inflammation in 1 patient and nodules in the other 2. Cases 5, 6, 7, 8, 9, 11, and 12 suggest acquired allergy, since reactions appeared for the first time only after a considerable period of treatment, and they increased in frequency or severity as the doses were continued. Approximately 16% of all the cases showed this kind of evidence of acquired allergy. When 1 patient who had acquired several hard nodules from previous subcutaneous injections of 2 cc. of thiomerin was given a similar dose intramuscularly, she developed general malaise with fever to 101°F., and with this, the lumps which were previously quiescent became red and tender and produced a sensation of "drawing". Another patient, Case 9 of Fig. 4, had several injections which resulted in small nodules. Then 1 dose caused a large area of local inflammation lasting more than 3 days. Three days later, a similar dose was given by intramuscular injection. There was no immediate reaction, but 4 hours later the patient developed severe pain in the thigh, with chill, and fever which rose to 102°F. The reaction gradually subsided in 36 hours.

Table 2 summarizes the data on the relation between the incidence of reactions and age of the solution. While the incidence turns out to be higher with the older solutions, the change in the total reactions which could be ascribed to the age of the solution would not be material, since the number of doses in these categories is relatively small. Figs. 3 and 4 also show that the age of the solution was not a significant factor in the high incidence of reactions.

This experience with the first group of 43 patients in whom an attempt

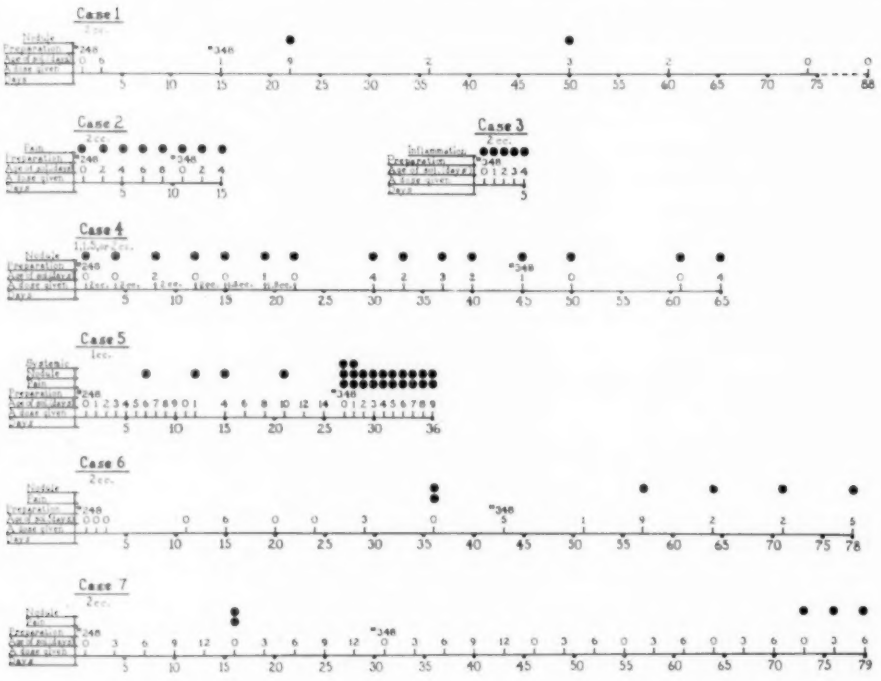


FIG. 3.—Cases illustrating patterns of local and systemic reactions to various regimens of thiomerin by subcutaneous injection.

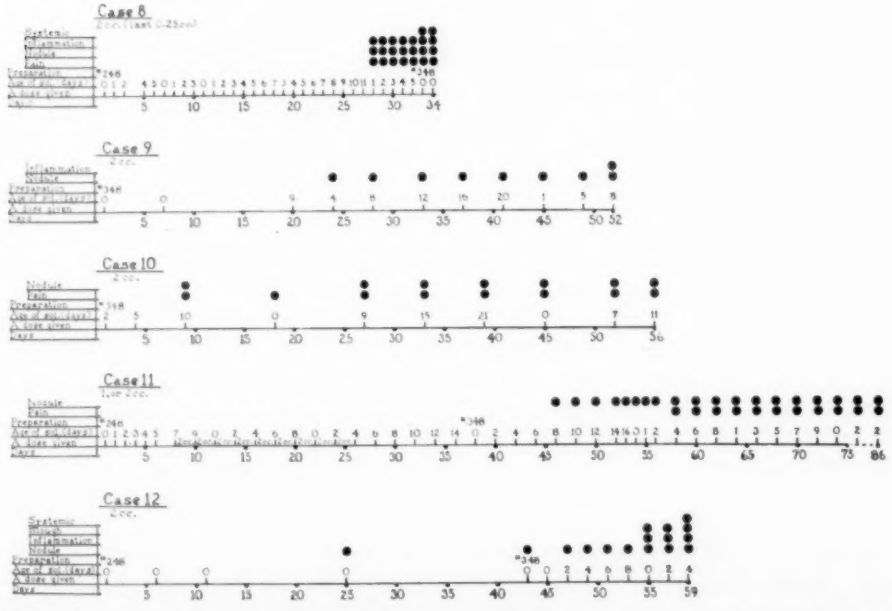


FIG. 4.—Cases illustrating patterns of local and systemic reactions to various regimens of thiomerin by subcutaneous injection.

TABLE 2.—RELATION OF INCIDENCE OF REACTIONS TO AGE OF SOLUTION

| *Age of solution* | *No. of injections* | *Injections which caused reaction* % |
|---|---|---|
| Fresh | 117 | 22 |
| 1–2 days | 122 | 25 |
| 3–5 days | 115 | 24 |
| 6–10 days | 85 | 32 |
| 11–21 days | 18 | 50 |

TABLE 3.—REACTIONS TO A SINGLE SUBCUTANEOUS INJECTION OF THIOMERIN IN 149 PATIENTS

| | *No. of Patients* | % |
|---|---|---|
| Patients with 1 or more reactions | 39* | 26 |
| Types of reaction | | |
| Pain | 16 | 11 |
| Inflammation | 10 | 7 |
| Ecchymosis | 2 | 1 |
| Nodule | 30 | 20 |
| Patients (observed 18 hours after injection, total 97) with 1 or more "early" reactions (began within 18 hours) | 4 | 4 |
| Types of reaction | | |
| Pain | 4 | 4 |
| Inflammation | 0 | |
| Ecchymosis | 0 | |
| Nodule | 0 | |
| Patients (observed 18 hours and 7 days after injection, total 63) with 1 or more "late" reactions (began after 18 hours) | 27 | 43 |
| Types of reaction | | |
| Pain | 9 | 14 |
| Inflammation | 6 | 10 |
| Ecchymosis | 1 | 2 |
| Nodule | 26 | 41 |

* Includes 8 patients in whom the time of onset of reaction was uncertain.

was made to pursue systematic treatment with thiomerin was discouraging. Intensive and prolonged systems of treatment in this group appeared to be a possible explanation of the higher incidence of reactions than reported by others. Accordingly, an attempt was made to determine whether the incidence of reactions in our hands would approach that of others in a group receiving only a single injection. This experiment was carried out in November, 1948. One-half of the patients received specimen No. 348, and the other half No. 548, a new lot of thiomerin which was said to be more stable than the previous ones. The subjects for this trial were 149 adult patients with chronic congestive failure, approximately an equal number of males and females, who had been in attendance at our clinics for periods of years. They had received mercuhydrin injections in doses of 1 or 2 cc. intramuscularly for at least 6 months at frequent intervals, some 1 injection a week, the majority 2 or more injections a week. In this group of 149 patients, the program of mercuhydrin injections was interrupted on one clinic visit and a similar dose of thiomerin was injected subcutaneously, in the arm in some of the cases, and in the buttock region in others. All injections

were made within an hour or less after the solutions were prepared. The local effect was ascertained a few minutes after the injection, from 12 to 18 hours later, and again on the patient's return to the clinic, usually within 1 week, and in a few cases within 2 weeks. Since the results with specimen No. 348 and No. 548 were similar, the data have been combined, and are summarized in Table 3.

There was not a single instance of appreciable reaction at the site of injection in the brief period from the time of injection until the patient's departure from the clinic. It may be noted, however, that in about one-fourth of the patients a local reaction took place, either in the form of severe pain, an inflammatory patch with redness and swelling, an area of ecchymosis varying in size up to that of a silver dollar, a fibrous nodule, or a combination of 2 or more of these reactions. It was noteworthy that of 97 patients who reported within 18 hours after the injection, only 4% showed reactions, while of the 63 of these who reported or were examined 7 days later, 43% showed reactions. As seen in Table 3, the incidence of pain beginning after 18 hours following the injection was nearly 4 times as high as that occuring earlier; ecchymosis occurred only after 2 or more days; and a hard nodule was observed only after 7 days.

In July, 1949, we received a fourth lot of thiomerin, control No. 029, stated to represent an improvement over previous materials and presumably the product of commerce. This was tried out in a new group of 38 patients in a manner similar to that in the group described above. The group represented an equal number of males and females with chronic congestive failure, who had been under treatment with mercuhydrin intramuscularly for from months to years. Again, the schedule for mercuhydrin was interrupted on one clinic visit and a subcutaneous dose of the thiomerin was substituted. Each vial of the new material yielded 30 cc. of solution and all injections were made within an hour after the solution was prepared. The dose was 2 cc. in 35 of the 38, and 1 cc. in the remaining 3 patients. The dose corresponded to that of the mercuhydrin they had been receiving. The injection was made in the upper deltoid region. It was made by one of the authors. In this group, information was obtained concerning reactions in the period from ½ to 20 hours (early reactions), and in the period of from 2 to 5 days (delayed reactions). The report of the patient and the result of the physician's examination were recorded separately. The data are summarized in Table 4. The results are essentially similar to those in Table 3. One or another, or a combination of local reactions, appeared in 37% of the cases. The observations within the first day were encouraging; only 8% had developed a local reaction when interviewed and examined within the period up to 20 hours after the injection. However, in a second interview and examination made in from 2 to 5 days, 26% additional cases with reactions appeared. In the 14 cases with reactions, there were 3 with nodules, 2 with tenderness, and 9 with ecchymosis. The nodules were seen during the examinations made within 20 hours in 2 cases, but not until the examination after 40 hours in the third case. They varied in size from a 5-cent to a 50-cent coin, and were still present a week after injection. One of these was moderately tender. Among the 9 cases with ecchymosis, 1 showed it on the first day; it was present in all cases by the end of the second day. These also varied in size from approximately a 5-cent to a 50-cent coin. None was tender. The delay in the appearance of

TABLE 4.—LOCAL REACTIONS TO A SINGLE SUBCUTANEOUS INJECTION OF THIOMERIN (CONTROL NO. 029) IN 38 PATIENTS

| | *Early—Appeared in ½ to 20 hr. Noted by* | | *Delayed—Appeared in 2 to 5 Days Noted by* | | *Total Reactions in 5 Days Noted by* | |
|---|---|---|---|---|---|---|
| *Type of Reaction* | *Patient* | *Physician* | *Patient* | *Physician* | *Patient* | *Physician* |
| | *No of Cases (%)* | | | | | |
| Patients with 1 or more reactions | 3 (8)† | 3 (8) | 4 (11) | 10 (26) | 7 (18) | 14 (37) |
| Ecchymosis | 1 (3) | 1 (3) | 3 (8) | 8 (22) | 3 (8) | 9 (24) |
| Nodule | 2 (5) | 2 (5) | 0 | 1 (3) | 2 (5) | 3 (8) |
| Tenderness | 1 (3) | 1 (3) | 1 (3) | 1 (3) | 2 (5) | 2 (5) |

† Figures in parentheses indicate percent of patients.

reactions in this group of patients is substantially similar to that observed in the previous group. More than 3 times as many reactions appeared on the second day or later than on the day of the injection. It is also to be noted that careful inspection of the site by the physician yielded twice as many reactions as reported by the patient.

**Discussion.** The studies in animals by Lehman and his collaborators[16,17,18] showing that mercaptomerin is virtually devoid of acute toxicity on the heart, and is less irritant to the skin and muscle than the conventional organic mercurial diuretic agents (combined with theophylline), have aroused considerable clinical interest. The fact that both its therapeutic and toxic actions appear to require dissociation of the compound, and the fact that, if sufficient time for this to take place is allowed, it develops toxicity similar to that of other organic mercurials, have not received sufficient attention[17]. There are the observations in dogs by Handley *et al.*[13] that thiomerin is more toxic than mercuhydrin as shown in various ways, namely, impairment of glomerular filtration (relatively greater reduction in creatinine clearance), and greater frequency of stomatitis, diarrhea, and fatal poisoning, which are ascribed to relatively slower and less complete excretion of the compound. Barrett[2] found thiomerin potentially more nephrotoxic than mercuhydrin in dogs. Capps *et al.*[6] found thiomerin more toxic than mercuhydrin and mercurophylline in chronic experiments in rats.

There are now several reports of experience with thiomerin, especially by subcutaneous injection, in patients with congestive failure. Since opinions relate both to its systemic and local actions, and these are compared with other mercurial diuretics, the brief review presented here will deal with the matter under these two headings. Not all reports have been included, but those which have been, we believe, suffice to reveal the present status of thiomerin with respect to systemic and local reactions.

Systemic Actions. Borg and Craig[5] treated 30 patients with subcutaneous doses of from 0.25 to 2.0 cc., usually 1 cc. The diuretic response was represented by a loss of weight of from 2 to 5 pounds. About one-third of their patients developed systemic symptoms, such as muscle cramps, prostration, and diarrhea, and these made it necessary to discontinue the drug in 4 patients. They ascribed these effects to excessive diuresis, preventable by using smaller doses. The patients were maintained on digitalis and ammonium chloride, preceding and during the course of treatment with thiomerin.

Ruskin *et al.*[20] compared thiomerin by subcutaneous injection, with mercuhydrin by intravenous injection in doses of 2 cc. They concluded that the diuretic effect was equal for equal mercury content in the doses. They stated that patients who developed nausea, vomiting, muscular cramps, and toxic psychosis after intravenous mercuhydrin tolerated thiomerin better.

Herrmann *et al.*[14] gave thiomerin by subcutaneous injection to 100 cardiac patients and stated that the diuretic response to thiomerin is not equal to that of other mercurials in the first 24 hours, but generally persists longer, for 2 or 3 days. They referred to one patient who developed a systemic toxic reaction from mercuhydrin intramuscularly, but who tolerated well thiomerin subcutaneously. This is a sample of a common experience, namely, that some patients are allergic to one mercurial diuretic but may take another member of the group without difficulty[9]. We were unable to draw any conclusions regarding relative diuretic efficacy from the data which were presented.

Batterman, Unterman, and DeGraff[3,4] reported experience with numerous doses of thiomerin in a large number of individuals comprising several groups of ambulant and hospitalized patients. The report by Batterman *et al.*[4] contains statements which suggest that their method for ascertaining relative diuretic efficacy of different compounds and by different routes of administration was not incapable of yielding them contradictory results. From one group (205 doses), they concluded that the diuretic effect of subcutaneous injection of thiomerin was as satisfactory as that of the intravenous or intramuscular injection of previous diuretics. Similarly, from another group (324 doses) they concluded that subcutaneous thiomerin was "in general" as effective as intravenous or intramuscular mercuzanthin or mercuhydrin. However, in the same report there is the opinion that, while subcutaneous thiomerin is equal in its diuretic effects to intravenous mercuzanthin, subcutaneous thiomerin is more potent than intramuscular mercuzanthin. Unless the method of comparison provides adequate statistical defenses against them, such contradictions may arise easily from the extreme variability in the diuretic response of different individuals to the same dose of the same compound. Examples are shown in the report by Modell *et al.*[19]: One patient who received 1 cc. of mercuhydrin intravenously (and essentially the same was true for mercuzanthin) at weekly intervals, lost 9, 5.5, and 2 lb., respectively, in the order listed; another lost 2.5, 4, 7.3, 2.5, 4, 4.8, 4, and 1.5 lb., respectively, in the order listed.

Attention may again be called to the fact that any statement regarding the relative potency of thiomerin and other mercurial diuretic agents must be based on a bioassay. None of the studies in the literature reports the use of a method which conforms to the standard requirements for a bioassay. We pointed this out in a recent paper on the bioassay of the mercurial diuretics in ambulant patients with congestive failure[11], and earlier in this report we presented results showing that the diuretic potency of subcutaneous thiomerin is substantially similar to that of intramuscular mercuhydrin which was used as the standard.

Local Reactions. Borg and Craig[5] observed local reactions in about 7% of the patients in the form of a sore nodule lasting more than a month and local tenderness lasting a week. They considered the incidence surprisingly low.

Ruskin *et al.*[21] observed slight tenderness in 4% and nodules in 6% in 50 patients who received 1 injection of 1 cc. of thiomerin. They found the incidence of these reactions higher in a group of patients who received 1 cc. of mercuhydrin subcutaneously.

Herrmann *et al.*[14] reported a 3% incidence of local pain and 2% of local infiltration. They referred to 1 reported case of slough after an intradermal injection and a similar reaction after injection into edematous skin. They stated that thiomerin is the only mercurial tolerated by subcutaneous injection, but Sussman and Stein[23] reported on more than 1000 subcutaneous injections of mercuhydrin in which this route was well tolerated in patients with congestive failure. We have reported a similar study which confirms this observation[25].

Batterman *et al.*[4] reported considerable local reactions, but wide differences in their experience with different groups. In 1 group, a dose of 1 cc. of mercuhydrin into the gluteal muscle caused "burning" pain for from 10 minutes to several hours in 60% of the cases (one case of induration in 24 hours); thiomerin caused similar complaints in 41% of the cases (no case of induration). The significance of this difference in small numbers of cases remains uncertain. In another group of 30 cases, doses of 1 and 2 cc. of thiomerin subcutaneously caused only slight "burning" for a few minutes. In still a third group of 143 patients (589 doses), with injections of 1 to 4 cc. of thiomerin subcutaneously, reactions noted were "burning" after 10% of the doses, tender induration after 4%, and nodules after 2.5%. They concluded that thiomerin by subcutaneous injection causes "minimal irritation". They expressed the view that the other mercurials in common use are "exceedingly irritant, necessitating deep intramuscular injections to avoid sloughs and excessive pain"; also that "many patients complain of pain, and nodule formation is not uncommon". One cannot be certain whether these comments refer to subcutaneous or intramuscular injection alone, or to all the mercurial diuretics (combined with theophylline) in common use. It has been our experience[10] that deep intramuscular injection of mercuhydrin almost eliminates manifest nodule formation. As for pain with the intramuscular route, the comparison of mercuzanthin and mercuhydrin by the "blind test" method in the study of Modell, Gold, and Clarke[19] showed, in 36 injections (20 patients) into various muscles of the upper and lower extremities, that in the case of mercuhydrin, pain sufficiently severe to arouse protest against repetition of the dose occurred after only 2.8% of the injections, "marked pain" after 2.8%, "moderate pain" after 8.3%, only barely perceptible discomfort after 30%, and no discomfort after 55% of the doses. The results expressed in terms of patients were as follows: Only 1 (5%) had very severe pain; 1 (5%) had marked pain; and the remainder (90%) had barely perceptible or no discomfort. This experience with intramuscular mercuhydrin compares favorably with that in the report of Batterman, Unterman, and DeGraff[4] that subcutaneous thiomerin is "well tolerated by patients in 90% of the trials". Reference has already been made to the studies which show that mercuhydrin exerts relatively little local irritation in most patients even after subcutaneous injection.

Grossman *et al.*[12] observed 2 cases of severe local reactions with subcutaneous thiomerin: in 1, pain, redness, and ulceration, and in the second a massive ecchymosis. They also noted small subcutaneous nodules at the site of injection in some patients who received re-

peated injections. Atkinson and Mulligan[1] treated 226 patients with congestive failure, and observed reactions in 35% of patients who received subcutaneous thiomerin.

Mention has been made of possible sloughs by the mercurial diuretics. These used to be fairly common. It is possible that they still occur after intravenous injections accompanied by thrombophlebitis resulting from perivenous infiltration. Our experience relates chiefly to mercuhydrin, although we have used some mercuzanthin and salyrgan-theophylline. In the period of many years since the development of the mercurial diuretics in combination with theophylline that are available in this country, and with our almost exclusive routine use of the intramuscular route, we have not encountered a single case of slough in an experience involving many thousands of injections. Thiomerin has revived the problem of slough. We have had 2 cases and a few are reported in the literature.

The evidence is abundant that thiomerin is not free of local irritation at the site of injection. The animal experiments of Lehman, Taube, and King[18] show that it gives rise to intense cellular infiltration and edema in rat muscle still present in 24 hours, and in some even after 96 hours, although the drug is allegedly absorbed in about an hour. A special feature of the results in these experiments is the fact that, unlike the reaction to mercuzanthin and mercuhydrin, the local effects of thiomerin after intramuscular injection in rats are completely reversible, and by subcutaneous injection in mice thiomerin causes no gross pathology, while mercuhydrin causes some necrosis. There is risk in the application of these observations to man, possibly because of difference in the response of different species, for in man, the local action of thiomerin is not completely reversible as shown by the occurrence of ecchymosis, fibrous nodules, and occasional slough.

Local Reactions not Eliminated by Current Preparations of Thiomerin. The above review of the literature indicates that the amount of local reaction differs with different observers. Clinical reports have shown a tendency to minimize the local reactions at the site of subcutaneous injection of thiomerin, and to assign most of the local reactions to earlier preparations of the drug. In connection with these points, it is useful to compare the report by Enselberg and Simmons[8] in February, 1950, with that by Krehbiel and Stewart[15] in May, 1951. Enselberg and Simmons reported on the results with 3314 subcutaneous injections of thiomerin in 205 patients. They stated that they encountered no local reactions after the fall of 1948. The report by Krehbiel and Stewart appeared more than 2 years after Enselberg and Simmons ceased to find local reactions, and involved material of more recent vintage. Their report refers to local reactions in about one-half of the patients, with the occurrence of subcutaneous nodules in 35% of their group.

Definition of Local Reactions. The incidence of local reactions was as high as 10% or more of the subcutaneous injections of thiomerin among the different reports. A comparison of the incidence of local reactions reported by various observers can prove misleading, however, because of the differences in criteria for a so-called local reaction. There is obviously no practical value in listing as a local reaction every symptom or sign at the site of injection. Many drugs widely used by injection give rise to a sharp sting, fairly protracted pain, or induration, but continue in use with little attention to these effects. Morphine, demerol, bismuth, and penicillin may be inclu-

ded among drugs causing such effects. The significance of the local reaction is worthy of attention. In this connection the temperament of the patient is involved. One patient might ignore a dime-sized ecchymosis or a fairly sharp pain, while to another such effects present a psychological hazard. We have seen occasional patients exhibiting concern over an isolated subcutaneous nodule, while others are untroubled by a state in which the arms and legs are studded with hard fibrous nodules rolling freely under the skin.

It seemed to us that the most useful information might be obtained if we counted as reactions only such responses at the site of injection as are sufficiently annoying or disturbing, or of such magnitude, severity, or duration as to create a problem which might constitute a threat to the continuation of the treatment. We employed this formulation with advantage in a recent study on the local reactions to the subdermal injection of mercuhydrin[25]. In the present study, the term "local reaction" does not refer, in the majority of cases, to a serious hazard, and often not even to an annoyance, but mostly to evidence of local tissue injury. The incidence of such local reactions in our experience is larger than that reported by others, namely, approximately 20% of all injections. More than one factor may account for these high values. We discovered that, in the case of thiomerin, 3 to 10 times as many reactions appeared after the second day as after the first. By our intensive system of administration, namely, doses at short intervals and sometimes daily, acquired sensitivity may appear. The possibility of such hypersensitivity was suggested by the report of Sulzberger, Baer, and Kanof[22], who showed that the application of BAL may sensitize the skin, and that cross-sensitivity may exist among the thiols. Our higher incidence of local reactions may also be accounted for, in part, by the fact that about twice as many are seen by the physician on inspection as are reported by the patient.

There is need for more experience and more careful observation before the place of thiomerin as a subcutaneous mercurial diuretic is established. A drug which needs to be given frequently over months or years by subcutaneous injection, and leaves some manifest tissue injury in its wake, has an unfavorable property.

The instability of thiomerin is a property which limits its utility. Current preparations of mercurial compounds combined with theophylline are more stable, and are relatively free of the danger of decomposition which results in highly irritant materials. In our recent study of subdermal injection of mercuhydrin[25], less than 10% of the injections and about 25% of the patients showed "troublesome" local reactions. The stability of this compound is a matter of considerable importance. In the case of less stable compounds like thiomerin, while the physician may be depended upon to inspect the solution for color or turbidity, and refrain from using a suspicious solution, there is the fact that the skill of the patient in this matter is not equally trustworthy.

In 1947 we formulated the need for self-injection of mercurial diuretics in the following manner[10]: ". . . there is the similarity between the problem of insulin in diabetes and the mercurial in congestive failure. In diabetes, it is not considered proper therapy to allow the patient to develop glycosuria, ketonuria, and symptoms, and then attempt to abolish them periodically by a dose of insulin. The plan for insulin is so worked out as to maintain the patient

free of symptoms, free of ketonuria, and free of glycosuria (or at a level of a constant moderate glycosuria). This now is the plan we advocate for the control of congestive failure, namely, the adjustment of the dose of the mercurial as well as the interval between doses in order to maintain a constant body weight after the optimum state has been established. Frequent injections often create a problem if a physician is necessary for all of them. We strongly urge, therefore, that a member of the family and sometimes the patient himself be instructed in the simple technique of an intramuscular injection after the physician has succeeded in establishing the proper maintenance program. The physician may then make periodic checks in order to determine any revision in the system which may become necessary." As we mentioned at the outset, the most important contribution of a subcutaneous mercurial diuretic to the control of congestive failure lies in the possibility of safe and convenient self-injection. Krehbiel and Stewart[15] tested the method of self-injection of thiomerin in 71 patients with congestive failure in their cardiac clinic. They concluded that subcutaneous thiomerin in the form in which it is now supplied on the market is useful for this purpose, although in their experience local reactions occurred in 53% of the patients (34% with pain lasting from 5 minutes to 2 days and 35% with subcutaneous nodules).

While thiomerin is a potent and substantially safe mercurial diuretic, the major problem in the treatment of congestive failure, for which there is need of a subcutaneous mercurial diuretic, does not appear to us to have been solved by the preparations that were available at the time of this and other recent studies.

**Summary and Conclusions.** 1. A new method of bioassay on ambulant patients with congestive failure shows that the diuretic potency of subcutaneous thiomerin is substantially similar to that of intramuscular mercuhydrin.

2. The view encountered in the literature that the action of thiomerin develops more slowly and lasts longer than that of other mercurial diuretics in common use was not confirmed in a comparison of thiomerin with mercuhydrin, both by subcutaneous administration, the effects being measured at 6 hours and 24 hours.

3. In the present study observations were made on the systemic and local reactions (at the site of injection) after 676 subcutaneous injections of thiomerin in 209 patients with congestive failure, with 4 lots of material, including 1 preparation of commerce. These fail to confirm the prevailing view that the local irritant actions produced by earlier preparations have been substantially eliminated from the more recent preparations. The results of the present study, and of others with the latest preparations of thiomerin, show that more than 25% of patients develop "troublesome" local reactions after subcutaneous doses.

4. The present study shows that the incidence of local reactions to thiomerin is increased if the subcutaneous dose is given more frequently (daily), if observations for delayed reactions (in 2 to 5 days) are made, and if the results are based on the physician's inspection rather than on the patient's report.

5. There is evidence of acquired allergy to thiomerin, probably due to the thiol portion of the compound.

6. Local reactions to subcutaneous thiomerin are not less frequent than local reactions to subcutaneous mercuhydrin.

7. While thiomerin is a potent and substantially safe diuretic agent, it is not sufficiently free of the risk of local reactions to meet the need for a mercurial diuretic for subcutaneous self-injection.*

The present study was supported in part by a research grant from the National Heart Institute, of the National Institutes of Health, Public Health Service, and in part by the Diuretic Fund of the Department of Pharmacology of Cornell University Medical College, to which contributions have been made by the Campbell Products, Inc., and the Lakeside Laboratories, Inc.

* Since this study was completed, it has come to our attention that still further changes have been made in the preparation which reduce the properties accounting for local reactions. In view of previous experience with these materials, decisions concerning diminished irritant properties should await the results of appropriate investigations in man.

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# PLASMA IRON:
# NORMAL VALUES; RESPONSE FOLLOWING MEDICATION

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The absorption, transport, and storage of iron has been the subject of many investigations both by chemical methods[7,11,12,15,17] and more recently by the use of radioactive or labeled iron[1,8]. The results of these various investigations have shown that ferrous iron is more readily absorbed from the upper gastrointestinal tract than is ferric iron[18] and it has been thought that absorption of iron from food is a controlled process[10], so that only a small amount of ingested iron is absorbed in a normal subject whereas a higher percentage is absorbed by patients with an iron deficiency anemia[19], but studies with radioactive iron do not entirely support this belief. Absorbed iron is transported in the plasma by a globulin fraction and Moore[16] has shown that there is no significant difference between plasma and serum iron levels, determinations of these levels being used as a measure of the absorbability of iron preparations. The normal serum iron levels range from 50 to 180 mcg. per 100 cc. Cartwright *et al.*[4] found the mean values to be almost identical for the two sexes, whereas Dahl-Sven[6] found the values to be slightly lower in women. Moore[19] found a range of 94 to 175 mcg. in males and 58 to 142 mcg. in women. During the course of investigations on various phases of iron metabolism we have accumulated data on this subject which seem worthy of presentation.

**Materials and Methods.** Blood samples drawn from the subjects were placed in oxalated bottles and centrifuged immediately to avoid hemolysis. Iron determinations were done in triplicate by the method of Kitzes, Elvehjem and Schuette[14]. The method was tested for accuracy by adding a known amount of iron to plasma of known iron content and ascertaining the total iron. These tests showed an average recovery of 100.9% and confirm the results of Cartwright.

Plasma iron determinations were made on 130 hospital patients whose hospitalization was the result of some condition which did not affect digestion, absorption or utilization of food, and which would not affect the plasma iron level. No patient with any type of blood dyscrasia or an infectious disease was included in this group. Blood was drawn from each subject at the same time of day—0900 hours—which was 2 hours after breakfast. Early in the investigation a special breakfast of constant iron content was served but this was discontinued when analysis revealed only a 3 mg. variation of food iron for the regular hospital breakfasts.

*Normal Values.* The results of plasma iron determinations are shown in Table 1. It will be noted that there is an extremely wide range of values, from 20 to 265 mcg. per 100 cc. of blood. The average figure for the entire group was 106.2 mcg. with a standard deviation of ±61.3. The

TABLE 1.—PLASMA IRON DETERMINATIONS IN 130 HOSPITAL PATIENTS

| No. | RBC Millions | Blood Hb Grams | Plasma Iron Micrograms % | No. | RBC Millions | Blood Hb Grams | Plasma Iron Micrograms % |
|---|---|---|---|---|---|---|---|
| 1 | 3.52 | 10.5 | 20.0 | 23 | — | 13.1 | 47.5 |
| 2 | 3.09 | 6.6 | 20.0 | 24 | — | 13.9 | 47.5 |
| 3 | 4.80 | 15.4 | 25.0 | 25 | 4.65 | 14.5 | 47.5 |
| 4 | 4.12 | 11.4 | 30.0 | 26 | 5.21 | 15.0 | 47.5 |
| 5 | 4.08 | 12.6 | 30.0 | 27 | 5.08 | 9.9 | 50.0 |
| 6 | 5.20 | 13.0 | 30.0 | 28 | 4.51 | 14.0 | 50.0 |
| 7 | 4.50 | 13.2 | 30.0 | 29 | 3.56 | 14.1 | 50.0 |
| 8 | 5.11 | 14.1 | 30.0 | 30 | 6.02 | 18.6 | 52.5 |
| 9 | 4.70 | 13.0 | 32.5 | 31 | 3.50 | 9.8 | 55.0 |
| 10 | 3.59 | 8.9 | 40.0 | 32 | 4.63 | 16.6 | 55.0 |
| 11 | 4.32 | 10.0 | 40.0 | 33 | — | — | 55.0 |
| 12 | 4.36 | 12.2 | 40.0 | 34 | 3.59 | 10.6 | 60.0 |
| 13 | 4.78 | 13.1 | 40.0 | 35 | 3.80 | 11.8 | 60.0 |
| 14 | 5.60 | 14.4 | 40.0 | 36 | 4.16 | 11.9 | 60.0 |
| 15 | 4.37 | 14.5 | 40.0 | 37 | 4.01 | 12.0 | 60.0 |
| 16 | 4.00 | 15.0 | 40.0 | 38 | 4.10 | 12.0 | 60.0 |
| 17 | — | — | 40.0 | 39 | — | 12.0 | 60.0 |
| 18 | 4.80 | 12.0 | 42.5 | 40 | 4.10 | 12.8 | 60.0 |
| 19 | 4.90 | 15.0 | 42.5 | 41 | 3.77 | 13.0 | 60.0 |
| 20 | 4.60 | 11.5 | 43.5 | 42 | 5.57 | 13.0 | 60.0 |
| 21 | 5.24 | 13.0 | 45.0 | 43 | 4.26 | 13.0 | 60.0 |
| 22 | 4.43 | 14.0 | 45.0 | 44 | 4.37 | 13.2 | 60.0 |
| 45 | 4.60 | 13.6 | 60.0 | 67 | 4.65 | 13.8 | 80.0 |
| 46 | 4.60 | 13.6 | 60.0 | 68 | 5.05 | 14.0 | 80.0 |
| 47 | 5.00 | 14.0 | 60.0 | 69 | 4.15 | 14.1 | 80.0 |
| 48 | 5.16 | 15.1 | 60.0 | 70 | 5.12 | 14.7 | 80.0 |
| 49 | 5.06 | 15.6 | 60.0 | 71 | 3.79 | 10.0 | 85.0 |
| 50 | 4.11 | 11.4 | 68.0 | 72 | 4.88 | 13.5 | 85.0 |
| 51 | 4.90 | 12.6 | 68.0 | 73 | 4.74 | 14.8 | 85.0 |
| 52 | 4.10 | 13.8 | 68.0 | 74 | 3.96 | 12.2 | 90.0 |
| 53 | 4.23 | 12.2 | 70.0 | 75 | 4.10 | 12.7 | 96.0 |
| 54 | 5.39 | 12.0 | 70.0 | 76 | 5.35 | 14.7 | 100.0 |
| 55 | 4.80 | 13.0 | 70.0 | 77 | 3.64 | 11.8 | 100.0 |
| 56 | 5.02 | 13.5 | 70.0 | 78 | 4.44 | 13.0 | 100.0 |
| 57 | 5.52 | 15.4 | 70.0 | 79 | 5.18 | 15.6 | 100.0 |
| 58 | 5.36 | 15.8 | 70.0 | 80 | 4.66 | 13.9 | 104.7 |
| 59 | 2.38 | 8.3 | 72.0 | 81 | 5.69 | 14.5 | 106.7 |
| 60 | 4.43 | 13.6 | 73.5 | 82 | 4.28 | 13.1 | 109.3 |
| 61 | 4.26 | 13.0 | 75.0 | 83 | 4.54 | 13.8 | 118.7 |
| 62 | 4.58 | 13.0 | 75.0 | 84 | 4.66 | 13.8 | 118.7 |
| 63 | 4.77 | 13.5 | 75.0 | 85 | 6.53 | 16.0 | 118.7 |
| 64 | 5.10 | 15.0 | 75.0 | 86 | 3.68 | 8.0 | 118.8 |
| 65 | 4.01 | 11.5 | 80.0 | 87 | 4.70 | 10.5 | 118.8 |
| 66 | 4.18 | 11.5 | 80.0 | 88 | 4.17 | 10.8 | 118.8 |
| 89 | 4.25 | 12.5 | 118.8 | 110 | 5.20 | 15.0 | 191.8 |
| 90 | 5.04 | 13.0 | 118.8 | 111 | 5.15 | 15.0 | 192.5 |
| 91 | 4.45 | 14.0 | 118.8 | 112 | 5.52 | 16.8 | 198.8 |
| 92 | 4.81 | 13.1 | 120.0 | 113 | 3.02 | 9.9 | 200.0 |
| 93 | 3.65 | 10.2 | 128.0 | 114 | 3.76 | 12.6 | 200.0 |
| 94 | 4.35 | 13.5 | 128.1 | 115 | 3.26 | 10.1 | 205.6 |
| 95 | 4.84 | 14.8 | 132.8 | 116 | 4.25 | 13.0 | 205.6 |
| 96 | 4.16 | 13.6 | 136.0 | 117 | 5.10 | 15.5 | 209.0 |
| 97 | — | 12.2 | 137.5 | 118 | 4.98 | 15.3 | 212.5 |
| 98 | 4.53 | 13.0 | 140.0 | 119 | 5.38 | 15.8 | 220.0 |
| 99 | 4.15 | 12.0 | 140.0 | 120 | 4.72 | 14.7 | 221.8 |
| 100 | 4.35 | 13.2 | 144.4 | 121 | 5.00 | 14.0 | 225.0 |
| 101 | 5.27 | 13.5 | 144.4 | 122 | 4.14 | 13.3 | 226.6 |
| 102 | 3.73 | 11.1 | 150.0 | 123 | 4.17 | 12.8 | 231.2 |
| 103 | 4.29 | 13.1 | 161.2 | 124 | 5.96 | 14.0 | 231.2 |
| 104 | 4.81 | 14.9 | 161.2 | 125 | 4.68 | 14.5 | 231.2 |
| 105 | 4.04 | 12.6 | 164.7 | 126 | 4.56 | 13.5 | 240.6 |
| 106 | 5.10 | 16.2 | 170.0 | 127 | 4.60 | 14.5 | 240.6 |
| 107 | 4.60 | 14.7 | 173.1 | 128 | 4.20 | 13.1 | 250.0 |
| 108 | 4.05 | 13.0 | 186.9 | 129 | 5.10 | 14.0 | 250.0 |
| 109 | 6.22 | 14.9 | 188.4 | 130 | 4.40 | 14.0 | 265.0 |

median was 83.3. These values show a somewhat wider range than has been reported by some but closely approximate the results of Cartwright who found a range of 28 to 210 mcg. with an average of 104.7 and a standard deviation of ± 32.8. Such wide ranges of normal values cast some doubt on the value of individual serum iron determination as a diagnostic procedure in various types of anemia or other blood dyscrasias. The serum values were slightly lower in women than in men (Table 2) as has been previously reported, the average for the women being 92 while that for the men was 111.2.

TABLE 2.—RANGE OF PLASMA IRON LEVELS ACCORDING TO SEX

| | *Number* | *Range* | *Median* | *Average* | *Std. Dev.* |
|---|---|---|---|---|---|
| Men | 89 | 20.0–265.0 | 82.5 | 111.2 | 67.9 |
| Women | 41 | 20.0–226.6 | 73.3 | 92.0 | 50.2 |
| | 130 | 20.0–265.0 | 81.1 | 105.5 | 63.4 |

*Effect of Gastric Acidity.* Similar plasma iron determinations were also made on 10 patients who had no free hydrochloric acid in their gastric contents after stimulation with histamine. The range of the plasma iron levels in these patients varied from 43.5 to 213.2. The average was 95.9 with a standard deviation of ± 60.25. The median was 74. The same determinations were done on a group of 23 patients having a normal gastric acidity. In those with a normal gastric acidity the average plasma iron value was 117.1 mcg. per 100 cc. with a standard deviation of ± 66.25 and a median of 74.3. By application of the t-test it was found that there is no significant statistical difference between the plasma iron level in those patients with achlorhydria, those with normal gastric acidity and those in the larger series in whom the gastric acidity was not determined. This agrees with the observation of Moore[17] who found that gastric acidity exerted no measurable effect on the absorption of iron salts.

*Values in Blood Dyscrasias.* In 14 patients with anemic or other types of blood dyscrasias, the plasma iron determinations were normal in all but 2 subjects. In 1 patient with a duodenal ulcer and anemia from hemorrhage a low plasma iron of 10 mcg. per 100 cc. was found. This is in keeping with the low values in iron deficiency anemias as reported by others. The highest value of 265.0 mcg. occurred in a patient with Cooley's anemia but a second case of Cooley's anemia had a plasma iron level of only 70 mcg. The plasma iron determinations were of no value in the differential diagnosis of these diseases. Cartwright[4] found a blood iron range of from 21 to 292 mcg. in a group of subjects with lymph node disorders and leukemia. He also noted a wide range of blood iron values in pernicious anemia and found a lowering of blood iron levels during the stage of rapid blood regeneration following therapy.

*Daily Variations.* In 20 subjects, the plasma iron was determined on 2 or more occasions on different days but under identical conditions and at the same time of day. The values are given in Table 3. It will be noted that although identical or very similar values were obtained in many cases, there are a few that show marked discrepancies between the readings, but all differences fall within the range of the standard deviation. The changes in the values were not constant in direction. Minor

TABLE 3.—RESULTS OF TWO PLASMA IRON DETERMINATIONS ON DIFFERENT DAYS

| | | *Plasma Iron mcg. %* | |
|---|---|---|---|
| *No.* | *Patient* | *I* | *II* |
| 1 | G. H. | 25.0 | 80.0 |
| 2 | M. J. | 104.6 | 40.0 |
| 3 | S. L. | 149.3 | 149.3 |
| 4 | S. J. | 60.0 | 67.5 |
| 5 | A. L. | 100.0 | 60.0 |
| 6 | G. F. | 120.0 | 73.5 |
| 7 | H. L. | 70.0 | 80.0 |
| 8 | G. B. | 70.0 | 80.0 |
| 9 | F. W. | 80.0 | 80.0 |
| 10 | H. J. | 80.0 | 96.0 |
| 11 | S. O. | 125.0 | 80.0 |
| 12 | B. C. | 80.0 | 137.5 |
| 13 | P. M. | 90.0 | 118.8 |
| 14 | C. C. | 104.7 | 100.0 |
| 15 | D. D. | 109.4 | 109.3 |
| 16 | G. M. | 137.5 | 161.3 |
| 17 | B. A. | 164.7 | 173.1 |
| 18 | M. F. | 185.0 | 198.7 |
| 19 | M. J. | 212.5 | 198.8 |
| 20 | A. D. | 265.0 | 265.0 |

fluctuations are not surprising since this plasma or transport iron must be in physiological equilibrium depending upon the amount being absorbed from the gastrointestinal tract, the amount being utilized by the bone marrow in hemoglobin synthesis, the amount being excreted and the amount being taken into the blood stream from the destruction of erythrocytes. Heilmeyer and Plötner[13] found a variation of ± 30% on repeated determinations and Moore[19] found a variation of 20 to 35 mcg. in a given day.

*Response Following Ingestion of Iron.* Iron salts were administered to patients with mild grades of iron deficiency anemias and the hemoglobin response and plasma iron levels were determined. The plasma iron determinations were done prior to the administration of iron and at 2-hour intervals thereafter for a period of 12 hours. It became apparent that the essential information could be obtained from the control determination prior to treatment and subsequent readings 4 and 6 hours later. This latter procedure was followed in subsequent patients. Three iron salts which we commonly employ in the therapy of iron deficiency anemias were tested in this manner to determine their effect on the plasma iron level. Plasma iron determinations were done at 0800 hours, 1200 hours and 1400 hours. A standard breakfast was given at 0700 hours. The iron was administered orally immediately after the plasma iron determination at 0800 hours. Table 4 shows the results in the control group who received no iron medication. In this group, as seen in Chart 1, there is an increase in the average plasma iron level at the end of 4 hours but a drop to, or near to, the original level by the end of 6 hours. There were 27 patients in this control group of patients.

Iron and ammonium citrates grains 15 were given to 20 patients and the resultant increase in the plasma iron level is shown in the chart. There was an initial increase in the plasma iron level during the first 4-hour period as was found in the control group, but there was an even more rapid increase

in the subsequent 2-hour period rather than a drop as was encountered in the control group. At the end of 6 hours the plasma iron level was markedly elevated. The data on the patients are given in Table 5.

to compare the effect of the drugs. In 2 instances Ferrocol® and iron and ammonium citrates were given to the same individual and in both instances the Ferrocol® produced a slightly higher plasma iron level at the end of 6

TABLE 4.—PLASMA IRON DETERMINATIONS IN 27 CONTROL PATIENTS RECEIVING NO MEDICATION

| | | | | *Plasma Iron—Micrograms Per Cent* | | |
|---|---|---|---|---|---|---|
| *No.* | *Patient* | *Sex* | *Age* | *0800 hrs.* | *1200 hrs.* | *1400 hrs.* |
| 1 | G. A. | F | 32 | 118.8 | 137.5 | 132.8 |
| 2 | M. A. | F | 48 | 85.0 | 148.7 | 124.0 |
| 3 | B. M. | F | 57 | 40.0 | 80.0 | 80.0 |
| 4 | S. R. | M | 74 | 118.7 | 152.8 | 90.0 |
| 5 | H. B. | M | 59 | 118.7 | 137.5 | — |
| 6 | R. C. | M | 50 | 60.0 | 80.0 | 50.0 |
| 7 | W. F. | M | 77 | 80.0 | 80.0 | 80.0 |
| 8 | J. M. | M | 69 | 40.0 | 47.5 | 50.0 |
| 9 | B. M. | M | 43 | 80.0 | 80.0 | 80.0 |
| 10 | J. S. | M | 45 | 60.0 | 100.0 | 100.0 |
| 11 | F. H. | M | 70 | 30.0 | 50.0 | 40.0 |
| 12 | F. F. | M | 67 | 60.0 | 60.0 | 80.0 |
| 13 | L. A. | M | 57 | 60.0 | 100.0 | 50.0 |
| 14 | M. L. | F | 22 | 50.0 | 50.0 | 75.0 |
| 15 | R. C. | M | 36 | 60.0 | 80.0 | 90.0 |
| 16 | V. G. | F | 18 | 40.0 | 52.5 | 40.0 |
| 17 | M. H. | M | 45 | 70.0 | 85.0 | 95.0 |
| 18 | M. R. | F | 57 | 40.0 | 58.0 | 57.5 |
| 19 | M. S. | F | 38 | 30.0 | 70.0 | 60.0 |
| 20 | C. A. | M | 59 | 30.0 | 55.0 | 47.5 |
| 21 | F. A. | M | 58 | 30.0 | 55.0 | 42.5 |
| 22 | L. S. | M | 36 | 55.0 | 75.0 | 60.0 |
| 23 | O. A. | M | 77 | 50.0 | 100.0 | 67.5 |
| 24 | G. L. | M | 46 | 45.0 | 80.0 | 50.0 |
| 25 | N. S. | F | 16 | 60.0 | 65.0 | 60.0 |
| 26 | G. Y. | M | 45 | 40.0 | 50.0 | 60.0 |
| 27 | W. K. | M | 69 | 118.7 | 137.5 | 113.7 |

Ferrocol®*5, a colloidal iron preparation, was given to 21 patients (Table 6) in a dose of 15 grains and a similar but slightly greater response was obtained than was encountered with iron and ammonium citrates. Ferrous sulfate (grains 15) in enteric-coated tablets† was given to 25 patients (Table 7) and this produced the least increase in the plasma iron levels of any of the drugs tested. A comparison of plasma iron response to the various preparations is shown in Chart 1.

In 11 instances 2 of the iron preparations were given to the same patient

hours. In 9 patients iron and ammonium citrate and ferrous sulfate were given to the same individual on different days. In 4 instances the iron and ammonium citrate produced the greater response; in 3 instances the response was greater with ferrous sulfate, whereas in 4 the difference was so slight as to be negligible (Table 8).

*Therapeutic Results.* The hemoglobin response following the administration of a preparation of colloidal iron (Ferrocol®) was studied in 2 groups of patients to determine its effects in comparison to other iron salts previ-

* Manufactured by Mulford Colloid Laboratories, Philadelphia; available in 5 grain capsules.
† Enseals, Lilly, or Feosol, etc.

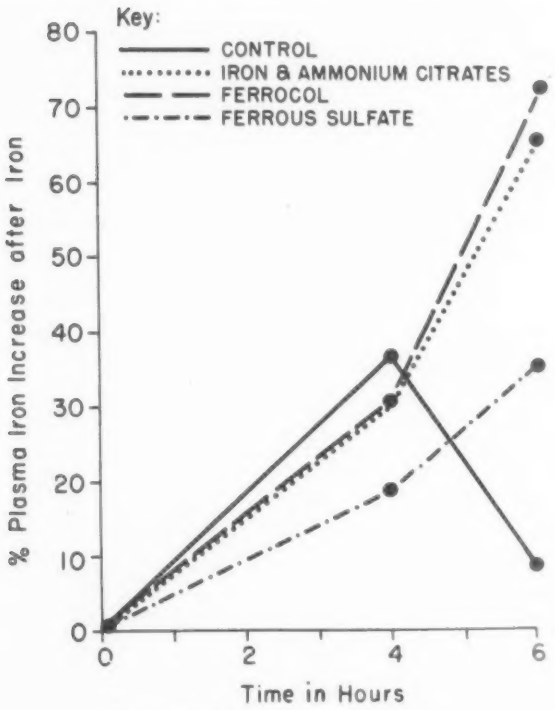


CHART 1. Increase in Plasma Iron.

TABLE 5.—PLASMA IRON DETERMINATIONS IN 20 PATIENTS RECEIVING IRON AND AMMONIUM CITRATES GR. XV

| | | | | *Plasma Iron—Micrograms Per Cent* | | |
|---|---|---|---|---|---|---|
| *No.* | *Patient* | *Sex* | *Age* | *0800 hrs.* | *1200 hrs.* | *1400 hrs.* |
| 1 | C. B. | F | 80 | 137.5 | 152.9 | 173.1 |
| 2 | H. G. | F | 79 | 80.0 | 109.4 | 70.0 |
| 3 | C. C. | F | 66 | 100.0 | 100.0 | 113.8 |
| 4 | M. G. | F | 47 | 161.3 | 195.3 | 210.3 |
| 5 | B. M. | F | 57 | 60.0 | 104.7 | 90.0 |
| 6 | M. P. | F | 43 | 118.8 | 212.1 | 257.5 |
| 7 | N. D. | M | 54 | 47.5 | 80.0 | 118.8 |
| 8 | V. B. | M | 55 | 52.5 | 119.4 | 160.7 |
| 9 | W. K. | M | 65 | 40.0 | 100.0 | 90.0 |
| 10 | D. D. | F | 27 | 109.4 | 131.6 | 188.4 |
| 11 | M. F. | F | 61 | 75.0 | 137.5 | 85.0 |
| 12 | M. H. | F | 45 | 75.0 | 137.5 | 167.2 |
| 13 | B. S. | F | 50 | 85.0 | 104.4 | 90.0 |
| 14 | J. B. | M | 69 | 42.5 | 70.0 | 80.0 |
| 15 | O. H. | M | 35 | 47.5 | 123.4 | 191.9 |
| 16 | L. H. | M | 57 | 70.0 | 114.1 | 137.5 |
| 17 | F. P. | M | 65 | 85.0 | — | 173.1 |
| 18 | C. C. | M | 59 | 70.0 | 180.7 | 185.0 |
| 19 | J. M. | M | 65 | 198.8 | 245.3 | 265.0 |
| 20 | F. M. | M | 67 | 185.0 | 198.7 | 212.5 |

TABLE 6.—PLASMA IRON DETERMINATIONS IN 21 PATIENTS RECEIVING FERROCOL GR. XV

| | | | | *Plasma Iron—Micrograms Per Cent* | | |
|---|---|---|---|---|---|---|
| *No.* | *Patient* | *Sex* | *Age* | *0800 hrs.* | *1200 hrs.* | *1400 hrs.* |
| 1 | P. H. | M | 63 | 30.0 | 62.5 | 80.0 |
| 2 | H. H. | M | 63 | 42.5 | 149.3 | 60.0 |
| 3 | M. D. | F | 76 | 118.8 | 140.9 | 217.1 |
| 4 | M. F. | F | 49 | 80.0 | 167.1 | 198.7 |
| 5 | A. S. | F | 50 | 45.0 | 52.5 | — |
| 6 | V. K. | F | 42 | 65.0 | 109.3 | 167.1 |
| 7 | M. Y. | M | 25 | 100.0 | 135.3 | 173.1 |
| 8 | B. B. | F | 28 | 60.0 | 109.3 | 123.4 |
| 9 | E. R. | F | 17 | 123.4 | 161.2 | 245.3 |
| 10 | M. R. | F | 36 | 85.0 | 114.0 | 137.5 |
| 11 | M. C. | F | 18 | 186.9 | — | 322.5 |
| 12 | B. D. | F | 17 | 144.4 | 152.8 | 197.5 |
| 13 | E. B. | F | 34 | 123.5 | 161.3 | 198.8 |
| 14 | M. M. | F | 34 | 205.6 | 217.2 | 268.8 |
| 15 | E. S. | F | 59 | 60.0 | 128.1 | 195.3 |
| 16 | W. C. | M | 37 | 60.0 | 104.7 | 123.4 |
| 17 | J. H. | M | 71 | 144.4 | 173.1 | 205.6 |
| 18 | G. H. | M | | 70.0 | 123.4 | 161.0 |
| 19 | J. M. | M | 65 | 212.5 | 231.3 | 280.0 |
| 20 | A. M. | M | 74 | 161.2 | 185.0 | 202.2 |
| 21 | F. M. | M | 67 | 198.7 | 231.3 | 250.0 |

TABLE 7.—PLASMA IRON DETERMINATIONS IN 25 PATIENTS RECEIVING FERROUS SULFATE GR. XV

| | | | | *Plasma Iron—Micrograms Per Cent* | | |
|---|---|---|---|---|---|---|
| *No.* | *Patient* | *Sex* | *Age* | *0800 hrs.* | *1200 hrs.* | *1400 hrs.* |
| 1 | N. B. | F | 62 | 118.8 | 158.8 | 118.8 |
| 2 | I. M. | F | 42 | 32.5 | 80.0 | 109.4 |
| 3 | F. N. | M | 49 | 42.5 | 50.0 | 50.0 |
| 4 | C. B. | F | 80 | 80.0 | 123.4 | 195.3 |
| 5 | H. G. | F | 79 | 25.0 | 50.0 | 80.0 |
| 6 | C. C. | F | 66 | 104.7 | 140.9 | 152.9 |
| 7 | M. G. | F | 47 | 137.5 | 179.0 | 191.8 |
| 8 | M. P. | F | 43 | 90.0 | 114.0 | 128.1 |
| 9 | D. | F | | 60.0 | 109.4 | 80.0 |
| 10 | M. | F | | 47.5 | 65.0 | 60.0 |
| 11 | M. D. | F | | 60.0 | 75.0 | 90.0 |
| 12 | D. D. | F | 27 | 109.4 | 118.8 | 140.9 |
| 13 | D. S. | M | 46 | 60.0 | 100.0 | 123.4 |
| 14 | R. S. | M | 70 | 100.0 | 118.8 | 173.1 |
| 15 | A. A. | M | 50 | 55.0 | 70.0 | 100.0 |
| 16 | H. G. | M | 64 | 188.4 | 191.9 | 212.5 |
| 17 | L. H. | M | 57 | 80.0 | 118.8 | 144.7 |
| 18 | H. L. | M | | 128.1 | 173.1 | 198.8 |
| 19 | W. B. | M | | 265.0 | 280.0 | 302.5 |
| 20 | H. M. | M | 61 | 240.6 | — | 272.5 |
| 21 | H. S. | M | 46 | 118.8 | 118.8 | 144.4 |
| 22 | J. W. | M | 60 | 212.5 | 244.3 | 240.6 |
| 23 | L. M. | M | 31 | 173.1 | 173.1 | 179.0 |
| 24 | C. J. | M | 62 | 144.4 | 195.3 | 198.8 |
| 25 | C. P. | M | 44 | 209.0 | 240.6 | 256.8 |

ously reported. It was administered to a group of 48 patients with mild degrees of iron deficiency anemia and to a group of 24 patients following blood donations. The response in these 2 groups is shown in Charts 2 and 3. Chart 2 shows the hemoglobin increase in 48 mildly anemic subjects. The response is satisfactory and compares favorably with the response to other types of iron medication which have been previously reported[9,2]. Chart 3 shows the hemoglobin response in 24 blood donors receiving Ferrocol® during the recovery period as compared to a similar number of blood donors receiving no medication. The response to this form of iron therapy is similar to that obtained with other iron preparations[3] under similar circumstances and shows a more rapid hemoglobin regeneration when iron therapy is given. Our interest in colloidal iron medication was aroused by the fact that we have encountered no gastrointestinal upset with this colloidal iron preparation in the dosages employed.

**Summary and Conclusions.** Plasma iron levels in 130 subjects ranged from 20 to 265 mcg. per 100 cc. of blood.

TABLE 8.—COMPARISON OF EFFECT OF IRON SALTS ON THE SAME PATIENT

| | | *Ferrous Sulfate Blood Plasma Iron Micrograms Per Cent* | | *Iron and Ammonium Citrate Blood Plasma Iron Micrograms Per Cent* | | *Ferrocol Blood Plasma Iron Micrograms Per Cent* | |
|---|---|---|---|---|---|---|---|
| *Patient* | *Sex* | *Initial* | *6 hrs.* | *Initial* | *6 hrs.* | *Initial* | *6 hrs.* |
| H. G. | F | 25.0 | 80.0 | 80.0 | 70.0* | | |
| A. A. | M | 55.0 | 100.0 | 60.0 | 167.2 | | |
| B. M. | F | 60.0 | 195.3 | 60.0 | 90.0 | | |
| L. H. | M | 80.0 | 144.7 | 70.9 | 137.5 | | |
| C. B. | F | 80.0 | 195.3 | 137.5 | 178.1 | | |
| M. P. | F | 90.0 | 128.1 | 118.8 | 257.5 | | |
| C. C. | F | 104.7 | 152.9 | 100.0 | 113.8 | | |
| D. D. | F | 109.4 | 140.9 | 109.3 | 188.4 | | |
| M. G. | F | 137.5 | 191.8 | 161.3 | 210.3 | | |
| F. M. | M | | | 185.0 | 212.5 | 198.7 | 250.0 |
| J. M. | M | | | 198.8 | 265.0 | 212.5 | 280.0 |

* 109.4 micrograms per cent at 4 hrs.

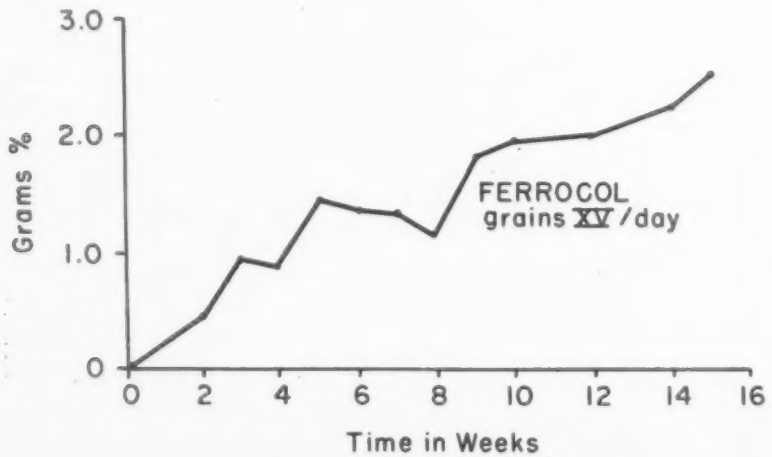


CHART 2. Hemoglobin Response in Mild Anemia.

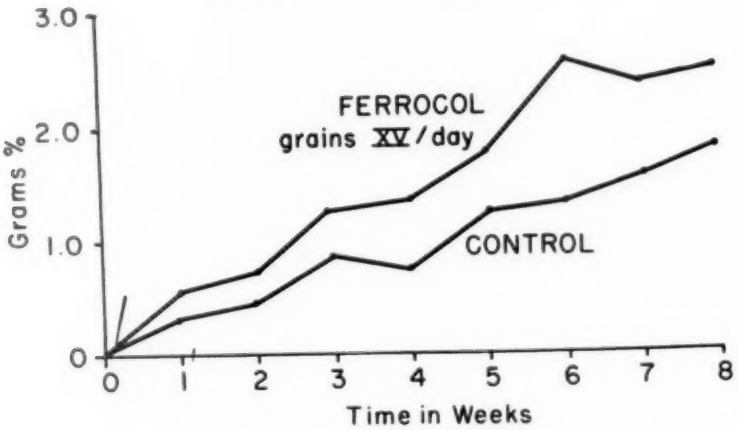


CHART 3. Hemoglobin increase in 24 subjects (blood donors.)

The values were slightly lower in women than in men.

There was no significant difference in the plasma iron levels in subjects with achlorhydria and in those with normal gastric acidity.

No variations of diagnostic significance were encountered in the various blood dyscrasias studied.

The oral administration of a colloidal iron preparation (Ferrocol®) produced a greater elevation of the plasma iron level and as rapid hemoglobin regeneration as was obtained with other commonly used iron salts when given to anemic subjects and to blood donors. Moreover, it did not produce gastrointestinal disturbances in any of the patients for whom it was prescribed.

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# THE USE OF RED CELL MASS IN RHEUMATOID DISEASE*

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Anemia as an associated phenomenon of rheumatoid disease has been recognized for many years[10]. Usually it begins insidiously, may become moderately severe as the disease becomes well established, and is of the normocytic or microcytic, hypochromic variety.

Clinical investigation of this feature has been mainly directed towards the etiological aspect. In our experience and that of others, the anemia of this disorder has been highly refractory to iron therapy[2]. Transfusions of whole blood have been recommended by several investigators[3,6,9,11] as adjunctive therapy, but they have noted no striking effect on the course of the disease. We thus became interested in the possibility of the existence of a dilution factor as the responsible mechanism, and so turned our attention from relative measurements of anemia as recorded by hemoglobin and hematocrit estimations to a critical study of blood and plasma volumes.

**Methods.** In order to eliminate sources of error so far as possible, blood and plasma volume estimations were made the responsibility of a single technician. The Crooke and Morris modification of the Gregerson dye method was used, and normal values were established for this laboratory. Serial hemoglobin, erythrocyte sedimentation rates, plasma protein estimations, and hematocrit readings were also made. Red cell counts were done only on specific request in a small number of patients, since the information obtained added very little to the required data.

Control studies on 50 apparently normal individuals gave the following average estimations (Table 1).

TABLE 1.—RESULTS OF CERTAIN BLOOD ANALYSES IN 50 NORMAL MALES

| | |
|---|---|
| Total Serum Proteins | 6.0–8.1 gm. per 100 cc. |
| Serum Albumin | 3.6–5.4 gm. per 100 cc. |
| Serum Globulin | 1.2–4.5 gm. per 100 cc. |
| Hemoglobin | 15.8 gm. (equivalent to 100%) |
| Hematocrit | 46–48% |
| ESR (Westergren) male | 0–20 mm. |
| Blood Volume | 85–95 cc./kg. body wt. |
| Plasma Volume | 40–46 cc./kg. body wt. |
| Thymol Turbidity | 4–5 units |

The purpose of this investigation was twofold: (1) to determine the basic mechanism of the anemia of rheumatoid disease, and (2) to observe the effect of transfusions of red cell mass on the hematologic pattern and the general condition of patients afflicted with this disorder.

The patients were those admitted to the Rheumatic Disease Section, Veterans Administration Hospital, Wood, Wisconsin. All patients have been treated in the period between 1948 and 1951. Follow-up records range between 3 months and 3 years. Most

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

of the patients had Stage II or Stage III illness (American Rheumatism Association classification).

The red cell mass was supplied by the Milwaukee Junior League Blood Center, and cross-matching and accurate assessment of all other factors were made routinely. Transfusions were given in courses of 4, 6 or 10 units. Each transfusion consisted of 1 unit of red cell mass (that is, the sedimented cells of 1 pint of whole blood after the plasma is withdrawn). Mild transfusion reactions were noted in only 2 cases.

volume in the atrophic group was 11.8% above the average for normal individuals, and that the increase in blood volume in atrophic arthritis was due to an increase in plasma volume which could not be explained on the basis of decreased body weight.

The results of our determinations made in the case of 25 normal male individuals showed the average whole

TABLE 2.—BLOOD VOLUME FIGURES AS DETERMINED IN 25 NORMAL MALES AND IN 25 MALES WITH RHEUMATOID ARTHRITIS

| *25 Normal Males* | | *Case No.* | *25 Rheumatoid Arthritics* | |
|---|---|---|---|---|
| *cc.* | *cc./kg.* | | *cc.* | *cc./kg.* |
| 6505 | 88.2 | 1 | 4916 | 81.9 |
| 4630 | 77.1 | 2 | 6557 | 93.6 |
| 8080 | 95.0 | 3 | 7304 | 104.2 |
| 5290 | 81.0 | 4 | 5653 | 94.2 |
| 8897 | 104.6 | 5 | 4551 | 75.8 |
| 6937 | 92.4 | 6 | 5306 | 88.2 |
| 5500 | 84.6 | 7 | 5250 | 87.5 |
| 7312 | 91.5 | 8 | 4310 | 71.8 |
| 8953 | 99.6 | 9 | 4583 | 76.3 |
| 7202 | 90.0 | 10 | 4500 | 75.0 |
| 7756 | 91.2 | 11 | 4910 | 81.8 |
| 7500 | 88.2 | 12 | 5041 | 84.0 |
| 7562 | 88.9 | 13 | 4435 | 73.9 |
| 6818 | 90.9 | 14 | 4741 | 79.0 |
| 7051 | 88.1 | 15 | 4981 | 83.0 |
| 7837 | 92.2 | 16 | 4714 | 78.5 |
| 7432 | 91.6 | 17 | 4789 | 79.8 |
| 6947 | 92.6 | 18 | 6486 | 92.6 |
| 7575 | 89.1 | 19 | 6117 | 87.2 |
| 6985 | 93.1 | 20 | 5789 | 89.1 |
| 6215 | 88.7 | 21 | 6694 | 95.6 |
| 6560 | 88.9 | 22 | 4959 | 82.6 |
| 4745 | 79.0 | 23 | 4004 | 72.8 |
| 5914 | 90.9 | 24 | 5360 | 82.4 |
| 5090 | 86.8 | 25 | 4267 | 77.5 |

**Results.** Thirty patients with rheumatoid disease treated by red cell mass transfusion and adequately followed up clinically and biochemically are considered in this paper. All patients showed an improvement in the levels of hemoglobin, sedimentation rate, hematocrit, and blood volume.

In 1932 Sparks and Haden[12] published their findings on blood volume studies in 26 patients suffering from atrophic arthritis (rheumatoid disease). They concluded that the average blood blood volume to be 89.7 cc. per kg., with a range from 77.1 cc. per kg. to 104.6 cc. per kg.; however, the blood volume of 20 of the 25 controls was between 85 and 95 cc. per. kg. For the 25 male rheumatoid patients the average whole blood volume was 83.2 cc. per kg.; the highest volume was 104.2 cc. and the lowest 71.8 cc. per kg.; in 16 cases the blood volume was between 70 and 85 cc. per kg. ,Table 2).

Increased plasma volume appears to be the mechanism accountable for the

TABLE 3.—PLASMA VOLUME FIGURES AS DETERMINED IN 25 NORMAL MALES AND IN 25 MALES WITH RHEUMATOID ARTHRITIS

| *25 Normal Males* | | *Case No.* | *25 Rheumatoid Arthritics* | |
|---|---|---|---|---|
| *cc.* | *cc./kg.* | | *cc.* | *cc./kg.* |
| 2667 | 35.5 | 1 | 2950 | 49.1 |
| 2365 | 39.2 | 2 | 4000 | 57.1 |
| 2750 | 32.2 | 3 | 4455 | 63.6 |
| 2750 | 42.3 | 4 | 3053 | 60.4 |
| 3025 | 35.5 | 5 | 3131 | 52.1 |
| 3330 | 44.4 | 6 | 3025 | 50.4 |
| 2530 | 38.9 | 7 | 2888 | 48.1 |
| 3218 | 40.2 | 8 | 2548 | 42.4 |
| 3850 | 42.7 | 9 | 2750 | 45.8 |
| 3025 | 36.5 | 10 | 2650 | 44.1 |
| 3025 | 35.5 | 11 | 2750 | 45.8 |
| 3000 | 35.2 | 12 | 3025 | 50.4 |
| 3025 | 35.5 | 13 | 2750 | 45.8 |
| 2250 | 30.0 | 14 | 2750 | 45.8 |
| 2750 | 34.3 | 15 | 2640 | 44.0 |
| 2557 | 30.1 | 16 | 2778 | 55.0 |
| 2750 | 34.3 | 17 | 3300 | 46.3 |
| 2640 | 32.5 | 18 | 3438 | 49.1 |
| 2499 | 29.4 | 19 | 3548 | 50.6 |
| 2375 | 31.6 | 20 | 3300 | 50.7 |
| 2300 | 32.8 | 21 | 3750 | 53.5 |
| 2225 | 29.6 | 22 | 3025 | 50.4 |
| 1993 | 33.2 | 23 | 2283 | 41.5 |
| 2207 | 33.9 | 24 | 3000 | 46.1 |
| 2035 | 33.9 | 25 | 2475 | 45.0 |

TABLE 4.—BLOOD AND PLASMA VOLUMES BEFORE AND AFTER RED CELL MASS TRANSFUSIONS IN 25 MALES WITH RHEUMATOID ARTHRITIS

| | *Before Red Cell Mass Transfusions* | | | *After Red Cell Mass Transfusions* | | |
|---|---|---|---|---|---|---|
| *Case* | *B.V.* (cc.) | *P.V.* (cc.) | % *P.V.* | *B.V.* (cc.) | *P.V.* (cc.) | % *P.V.* |
| 1 | 4916 | 2950 | 60 | 5675 | 2238 | 39 |
| 2 | 6547 | 4000 | 61 | 7051 | 2750 | 39 |
| 3 | 7304 | 4455 | 60 | 7875 | 3258 | 41 |
| 4 | 5625 | 3053 | 54 | 6215 | 2300 | 36 |
| 5 | 4551 | 2731 | 60 | 5081 | 1985 | 39 |
| 6 | 5306 | 3025 | 57 | 7312 | 3218 | 44 |
| 7 | 5250 | 2888 | 55 | 6163 | 2529 | 41 |
| 8 | 4310 | 2548 | 57 | 4904 | 2083 | 42 |
| 9 | 4583 | 2750 | 60 | 5341 | 1990 | 37 |
| 10 | 4500 | 2650 | 59 | 5626 | 2184 | 39 |
| 11 | 4910 | 2750 | 56 | 6237 | 2097 | 33 |
| 12 | 5041 | 3025 | 60 | 6308 | 2321 | 36 |
| 13 | 4435 | 2750 | 58 | 5945 | 2102 | 35 |
| 14 | 4741 | 2750 | 58 | 6014 | 2575 | 42 |
| 15 | 4981 | 2641 | 53 | 5741 | 1889 | 32 |
| 16 | 4714 | 2778 | 58 | 6464 | 2425 | 37 |
| 17 | 4789 | 2900 | 60 | 5500 | 2022 | 36 |
| 18 | 6486 | 3438 | 53 | 7314 | 2530 | 34 |
| 19 | 6117 | 3548 | 58 | 6560 | 2723 | 41 |
| 20 | 5789 | 3300 | 58 | 6567 | 2871 | 43 |
| 21 | 6694 | 3750 | 56 | 6985 | 2410 | 34 |
| 22 | 4959 | 3025 | 61 | 6215 | 2486 | 40 |
| 23 | 4004 | 2283 | 57 | 5500 | 1992 | 36 |
| 24 | 5360 | 3000 | 56 | 7202 | 2355 | 32 |
| 25 | 4267 | 2475 | 58 | 7475 | 2999 | 40 |

anemia. In the rheumatoid individuals the plasma volume ranged between 41.5 cc. and 63.6 cc. per kg., and averaged 48.9 cc. per kg.; as compared with a range of 29.6 cc. to 44.4 cc. per kg. in normal individuals, with an average of 36.0 cc. (Table 3).

Before transfusion, plasma volume range was noted as 53 to 62% of the total blood volume. Within 1 week following the course of red cell mass transfusions, the range was between 32 and 44% of the total blood volume (Table 4).

Clinical improvement, both objective and subjective, was seen in every patient receiving red cell mass transfusions. This response was evident in 24 hours in 3 cases, 48 hours in 10 cases, 3 days in 6 cases, 4 days in 3, 5 days in 3, 6 days in 2, 7 days in 1, and 9 days in 2. Four of the group of 30 showed good hematologic and only fair clinical response, however. The patients stated that they felt generally much better, pain and stiffness became minimal, appetites improved, range of motion was increased, and they were able to rest more comfortably. Swelling, tenderness, nodules, and muscle spasm decreased. No evidence of increased diuresis was observed and no changes were noted in the Roentgen-ray appearance of involved joints. Two of the patients had an associated psoriasis which demonstrated no change in the lesions following treatment, and 2 had ankylosing spondylitis, rheumatoid type, that exhibited clinical and laboratory improvement. One case with coincidental intermittent hydrarthrosis had good response so far as his rheumatoid disease was concerned, but the hydrarthrosis remained unaffected: this patient has since been treated with cortisone and again the intermittent hydrarthrosis has been unaltered. Another case presenting Reiter' syndrome was favorably affected by red cell mass transfusions.

During the past year, 5 cases have been seen in relapse. Twenty-five patients who have received courses of red cell mass have not returned to the hospital, and on questioning by letter or personal interview have said that they have remained in reasonably comfortable remission. Of the 5 relapsed patients, one required 3 courses of red cell mass over a period of 4 months, but has remained in remission for the past year.

Controls. A control group of 30 patients with similar stages of rheumatoid disease was used for comparative study. They were admitted to the Veterans Administration Hospital, Wood, Wisconsin, prior to 1948 and received all other forms of treatment then available, save blood or blood product transfusions. Evaluation in terms of hematopoietic and clinical response showed 54% improved, 33% unimproved, and 13% worse. By comparison, the treated cases showed 83% improved, 10% unimproved, and 7% worse. Response to treatment as reflected by change in sedimentation rate, hemoglobin, hematocrit, and blood volume was manifestly much better, both as to rapidity and quality, in the patients receiving red cell mass transfusions. Serum proteins and thymol turbidity reverted to normal in almost all instances within 1 week after the start of treatment. Clinical changes in the improved cases were observed within 4 days after therapy began in 22 cases and within 9 days in the remaining 3; in the controls, clinical changes of the same magnitude were observed in not one case in less than 12 days and laboratory improvement rarely was seen before two weeks on the usual regime.

**Discussion.** The transfusion of blood products has been employed by some

physicians in the treatment of rheumatoid disease since 1930 [3,4,11]. A number of observers, using 1, 2 or more small transfusions of whole blood in the active case with moderately severe anemia, noted a mild to moderate response in the hematopoietic picture[6,9]. Subsequently, and particularly since 1949, when the reversibility of certain stigmata of the disease was re-emphasized[8], interest was stimulated in the employment of blood products. This phase was characterized by the utilization of sera, plasma and/or whole blood from individuals affected by certain phenomena related to the relief of clinical evidences of rheumatoid disease, namely jaundice and pregnancy states[7].

Presumably the benefits to be derived from the blood of jaundiced patients were associated with the restitution of alterations observed in the serum lipids, phospholipids, and cholesterol, free and esterified, of rheumatoid patients. However, such changes were not predictably present nor uniformly reproducible. Furthermore, treatment with this type of blood was unattended by the anticipated good results.

Reports of a limited number of patients who allegedly obtained good therapeutic response from administration of blood from pregnant donors was made by Barsi[1]. The rationale of this type of therapy is contained in the observation that remissions of rheumatoid disease occur during pregnancy; but since not all pregnant females with rheumatoid disease remit, and since relapses occur following pregnancy in those who do have remission, it is difficult to see why blood transfusions from pregnant women should have any permanent effect.

We have noted with interest the clinical improvement that has rapidly and almost uniformly attended the introduction of this therapy. The effects are apparently unrelated to the nature of the source of the red cell mass; whether male or female, pregnant or virginal, fetal or senile. Why these effects occur and what may be the physicochemical mechanism responsible for them, remains unanswered; but work is going forward in our laboratory at the moment which we hope will throw some light on the reason for the changes being wrought.

At this time we employ the following criteria as indications for red cell mass transfusions:

(1) active disease which does not respond to other usual forms of treatment;
(2) hemoglobin estimations under 11 gm., or hematocrit readings below 40%.

**Summary.** Total blood volume was somewhat higher in 25 normal individuals than in 25 rheumatoid patients but the most significant observation was the finding of a substantial increase in plasma volume in the rheumatoid as compared to normal individuals.

The anemia of rheumatoid disease appears to be due to an increase in the plasma volume. Transfusions of red cells restore the normal cell-plasma relationship and thus constitute a useful supplement to our therapeutic armamentarium.

Red cell mass transfusions should be employed with greater frequency in the management of the rheumatoid patient.

A course of not less than 6 and not more than 10 units, given as 1 unit

daily, will produce the most beneficial results; such courses may be repeated as required.

While this form of treatment has proved both economical and satisfactory in our experience, it should be remembered that the dangers of transfusion reactions are ever present and great care should be exercised in the use of red cell mass therapy.

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# RHEUMATIC FEVER DURING THE FIRST FEW YEARS OF LIFE AND ITS DIFFERENTIATION FROM ENDOCARDIAL FIBROSIS

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Recent experience with 26 cases of rheumatic fever occurring at age 5 or at an earlier age suggests that the disease is more common in this group than previously suspected. Much of the difficulty of recognition arises from: 1) a preconceived and erroneous idea that it is non-existent in the first few years of life; 2) overemphasis of rigid diagnostic criteria; 3) the natural assumption that all murmurs found in the first few years of life are congenital in origin; 4) the frequent similarity of endocardial fibrosis.

**Analysis of Material.** The diagnosis of rheumatic fever and rheumatic heart disease was established in 4 cases by autopsy. The remaining 22 cases were diagnosed by the presence of characteristic features of rheumatic infection or the development of rheumatic heart disease after a long term followup.

**Case Reports.** Case 1. J. G. M., female, age 4, was admitted to the hospital in a critical state. For 2 years the child had been observed to have a fast pulse. Three months prior to admission she had complained of aching ankles and knees, and rheumatic fever was suspected. Two and a half months before admission she noticed black and blue spots, swelling and tenderness of the knees. Ten days before admission she noted an increase in pain in the legs and joints of the lower extremities, and 2 days prior to admission she developed dyspnea, and abdominal and pedal swelling. The patient was pale, dyspneic, and slightly cyanotic. The temperature was 98.2° F.; pulse, 190; respiration, 50; blood pressure 120/90. Cervical and axillary lymphadenopathy were noted. The neck veins were greatly distended, and there was some left-sided chest enlargement. There were dullness, diminished breath sounds, and moist rales over the left lower lobe. The heart was greatly enlarged, and the point of maximal impulse was in the sixth left interspace in the anterior axillary line. The rhythm was regular, but extremely rapid. A loud systolic murmur and a loud diastolic rumble were heard at the apex. The abdomen was distended with fluid, and the liver edge was felt 10 cm. below the right costal margin in the right midclavicular line. There was 2 plus pedal edema, and the nail beds were cyanotic. Despite oxygen, digitoxin, and mercuhydrin, she drew progressively worse and died within a short while.

On pathologic examination the heart weighed 150 grams, and all chambers were markedly dilated. The myocardium was pale, reddish brown in color, and soft in consistency. The endocardium throughout the heart was slightly opaque; this was most marked in the left atrium. The endocardium of the left atrium showed a yellowish-grey color, particularly on the posterior wall. The tricuspid and pulmonary valves showed no abnormality. The mitral valve showed, at its approximating surfaces, a small row of firm, saw-toothed like projections which had a slightly yellow color. The valve leaflets

* Presented at the meeting of the American Heart Association, Atlantic City, N. J., June 8, 1951.

were thickened and shortened and the chordae tendinae showed some coalescence and shortening. The aortic valve showed slight thickening of the base of the valves. Microscopic examination of the myocardium showed an unusual amount of rheumatic activity. Every fibrous septum was involved by an Aschoff nodule in some form of development. These nodules for the most part were located near blood vessels. Areas of acute necrosis of the myocardium were seen, and there was a great deal of involvement of the papillary muscles. No rheumatic pericarditis was seen. The remainder of the gross examination revealed bilateral massive hydrothorax and ascites. The lymph nodes throughout the mesentery were markedly enlarged as were the lymph nodes throughout the body. Upon cut section the lymph nodes showed raised, greyish areas which were interpreted as representing hyperplastic lymphoid follicles. On microscopic section many of the lymph nodes showed acute hyperplasia with focal necrosis of the lymphoid follicles and were infiltrated by polymorphonuclear leukocytes. The remaining organs showed evidence of severe congestive heart failure.

COMMENTS. Rheumatic activity probably began at age 2 when tachycardia was first noted. Joint symptoms before age 4 aided in the diagnosis of rheumatic fever. Evidence of carditis characterized by cardiac enlargement, systolic and diastolic apical murmurs, and congestive failure made its appearance in the early part of her 4th year of age. The autopsy was unusual in that there was such extensive rheumatic involvement of the myocardium and a marked degree of lymphadenopathy.

CASE 2. B.D., a female, age 5, was admitted to the Grady Memorial Hospital on July 17, 1947. Orthopnea, tachycardia, and facial edema had been present for 1 month. The facial swelling increased, and pedal edema developed. There was no history of previous respiratory infection or rheumatic fever. The child was pale, dyspneic, and orthopneic. The temperature was 100.5° F.; pulse, 160; respiration, 88; and the blood pressure was 95/80. The heart was enlarged to the left anterior axillary line. There was lifting of the lower sternum with each cardiac systole, and there was a diffuse apical impulse. An intense systolic thrill was felt at the apex. There was a harsh, loud systolic murmur replacing the mitral first sound, and a faint low-pitched diastolic rumble. The liver was enlarged 5 cm. below the costal margin. There were signs of bilateral pleural effusion. Laboratory studies repeatedly showed a normal urine with low specific gravity. At the time of admission the white blood count was 8,700 with a normal differential. The red blood count was 5,000,000, and the hemoglobin was 12.8 gm. The sedimentation rate on admission was 52 mm. per hour. Several blood cultures were sterile. A throat culture showed beta-hemolytic streptococcus. Roentgenograms showed cardiac enlargement with mitral configuration, pulmonary congestion, and slight bilateral pleural effusion. Several electrocardiograms were made, and the P-R interval was never prolonged, but the Q-T interval was 0.28 at a rate of 140. The magnitude of the ventricular complexes suggested generalized ventricular hypertrophy. There was fever which responded to aspirin, but in spite of routine therapy there was progressive congestive heart failure with death occurring 53 days after admission.

On pathologic examination the heart weighed 190 gm., and all chambers were markedly dilated. There were subepicardial hemorrhages. The myocardium was pale pink in color and flabby in consistency. A MacCallum's patch was noted on the posterior surface of the left atrium above the mitral orifice. The tricuspid and pulmonary valves were entirely normal, but the aortic valves appeared edematous. The mitral leaflets were considerably thickened and shortened and were slightly fused together. Microscopic examination of the sections from the ventricles, left atrium, and all valves showed the lesions of acute rheumatic carditis. Aschoff bodies were seen in the interstitial connective tissue, and tended to arrange themselves perivascularly. The collagenous tissue appeared smudged and was highly eosinophilic and presented the usual picture of fibrinoid degeneration. Numerous Aschoff bodies were noted in the MacCallum's patch. There was so-called rheumatic pneumonitis in sections of the lungs.

COMMENT. Myocarditis with congestive heart failure was the main manifestation of rheumatic fever in the above case. Edema of the face was one of the early signs of heart failure. The loud apical systolic and rumbling apical diastolic murmurs were quite

characteristic of rheumatic myocarditis. It is interesting that the sedimentation rate was within normal range a short while before death even though the evidence of congestive heart failure was steadily increasing.

CASE 3.* J. R., male, age 7, had frequent colds and fever during the first year of life. At age 1 he was found to have an enlarged heart and murmurs which were thought to be of congenital origin. There were frequent attacks of tonsillitis and upper respiratory infections with lagging of physical development. Congestive heart failure with mild cyanosis occurred at age 3. This responded well to digitalis, but he continued to have frequent bouts of tonsillitis and heart failure. The heart was markedly enlarged, and there was a left-sided chest deformity. A loud rough systolic murmur and thrill were heard over the entire precordium, and this was loudest at the base. There were loud systolic and diastolic murmurs at the apex, but the rate was so rapid that the beats were thought to be almost continuous. There was pulmonary congestion and enlargement of the liver. The patient died of severe heart failure at age 7. At no time during his illness were there joint symptoms.

Pathologic examination showed marked hypertrophy and dilatation of both ventricles. The wall of the left ventricle measured 1½ cm. The mitral valve was rigid and stenosed with a diameter of 1 cm. There were no vegetations. The lungs were almost solid with reddish-brown patchy consolidation involving four-fifths of the lung volume. The uninvolved areas were wet and edematous. Microscopic examination showed hemorrhagic congestion with engorgement of the capillaries with blood. The alveoli were full of red blood cells with a few mononuclear cells and polys. The liver and spleen were twice normal size. There was marked central congestion of the liver. The autopsy was done in a neighboring city and sections of the heart muscle were discarded by error.

COMMENT. This patient was found to have valvular heart disease at age 1 and subsequently developed chronic congestive heart failure. It is probable that he had active rheumatic infection for most of his life. There were never any joint symptoms. At autopsy there was marked stenosis of both the mitral and aortic valves. Although the lesion was originally thought to be of congenital origin, the characteristic murmurs should have led to a diagnosis of rheumatic heart disease.

CASE 4. L.B., colored male, age 5, was admitted to Grady Memorial Hospital August 16, 1948. He had a history of migrating polyarthritis for 1 or 2 months prior to admission associated with fever and occasional epistaxis. These joint symptoms occurred 1 to 2 months prior to admission, and following this edema of the feet and face occurred. He also complained of dyspnea and palpitation and was finally admitted to the hospital in acute respiratory distress. Physical examination: the heart was markedly enlarged; the liver and spleen were palpable. The heart rate was 120 and was regular. P2 was extremely loud and M1 was accentuated. There was a rumbling diastolic murmur heard at the apex transmitted to the axilla. There was a grade 4 systolic murmur heard over the entire precordium. Diastolic tricuspid and diastolic aortic murmurs were audible. Rales were present in both lower lung fields. There was progressive congestive heart failure and low grade temperature. Laboratory data revealed a hypochromic anemia, and the sedimentation rate ranged between 30 and 50. Urinalysis was negative. The electrocardiogram showed a ventricular rate of 130, P-R interval .16, Q-T interval .28, right axis deviation with large broad P waves. Fluoroscopic examination revealed marked generalized enlargement and definite left atrial enlargement. Several electrocardiograms were made, and during one period nodal rhythm was present. The patient was discharged from the hospital because of crying and complete unhappiness. He was managed at home on digitoxin and mercuhydrin, bed rest, and low salt diet. He was readmitted to the hospital on February 2, 1949, because of severe congestive failure. The neck veins were markedly distended, and rhonchi and wheezes were heard throughout both lung fields. The heart was markedly enlarged to the anterior axillary line, and the murmurs remained the same as previously described. He had had an upper respiratory tract infection one month prior to final admission. Hemoglobin on this admission was 12.3 gm.

On pathologic examination the heart weighed 210 gm. (normal 85 gm.). The left

* Case used through the courtesy of Drs. Sam and Harvey Howell, Cartersville, Ga.

atrium and left ventricle were dilated with marked bulging of the interventricular septum into the cavity of the right ventricle. The endocardium was thin, smooth, and glistening except for a rough patch in the left atrium. The myocardium was soft, yellow, and flabby. There was patchy pericardial thickening. Microscopic examination showed diffuse edema of the interstitial tissue with acute interstitial myocarditis. This was most pronounced in the interventricular septum. The mitral valve was thickened with areas of collagenous tissue degeneration surrounded by polymorphonuclear leukocytes and lymphocytes. These were interpreted as subsiding Aschoff nodules and similar lesions were noted in the right ventricular myocardium.

(CASES 5 to 26, inclusive). These cases were considered to have clinical evidence of rheumatic fever or rheumatic heart disease. For brevity, the cases are not reported in detail,* but the significant features are included in Table 2 with data of the autopsied cases.

**Discussion.** Statistical analysis of the incidence of rheumatic fever indicates that the disease is rare under the age of 5, Hedley reporting 5% of 1324 cases in this age group[7]. This, however, does not warrant the impression that it is almost non-existent then, since there are numerous reports of rheumatic fever under that age[4,5,6,10,12,13]. McIntosh and Wood[9] reported 24 cases of rheumatic fever occurring during the first 3 years of life, and Poynton[11] reported 52 cases under 5 years of age. There have been rare reports of infection in the newborn[3]. The determination of the age of onset is notoriously difficult; for example, a child at 7 with obvious rheumatic fever may give a history of suggestive, but non-diagnostic, symptoms at age 4. What is the actual age of onset? The suspected age of onset in the present series of cases is shown in Table 1.

The symptoms and signs of rheumatic fever occurring in this series are shown in Table 2.

A history of frequent upper respiratory infection occurred in less than half of the cases. Some experienced repeated attacks of "pneumonia" which, on occasion, were probably episodes of rheumatic myocarditis with pulmonary congestion or a combination of both diseases. Many children had episodes of high fever for a few days with low grade fever for weeks or months thereafter.

Fever occurred frequently, but fever alone should not be the basis for the diagnosis of rheumatic fever. It should be recalled that even in this age group neurogenic fever may be a source of confusion. Abdominal pain occurred in about 1/3 of the patients and at times it may simulate appendicitis. Most of the abdominal complaints were vague and ill-defined and assumed importance only in retrospect. Non-traumatic epistaxis was infrequent. The complaint of aching joints occurred in 19 patients, but objective evidence characterized by hot, swollen, tender joints was present in only 9. Sudden onset with refusal to walk was noteworthy in several instances, and in one case led to an erroneous diagnosis of poliomyelitis. None had joint deformity or residual stiffness. Chorea was suspected in only 1 patient. Skin manifestations were unusual, but when erythema marginatum or subcutaneous nodules occurred they were of diagnostic value. The patient with subcutaneous nodules had recurrent crops which occurred explosively over the scalp, forehead, chest, and extremities.

As in other reported series, the most frequent diagnostic manifestations were those of carditis or valvular heart disease. Significant systolic murmurs at the apex were present in 22 cases. A low-pitched mid-diastolic rumble was present at the apex in more

* The case reports in detail will appear in the authors' reprints.

than one-half of the cases. This murmur had definite duration and was distinct from physiologic third heart sounds. A middiastolic rumble occurring early in the course of the disease was interpreted as evidence of active myocarditis, whereas those occurring in the absence of enlargement or clinical evidence of activity were thought than one-half of the patients. Enlargement of the left atrium was noted in 9 of 19 cases. This enlargement usually is due to mitral stenosis but at times may be due to rheumatic myocarditis. Congestive heart failure was present in 11 patients. The electrocardiogram was of little diagnostic help, although there were P-R prolongation in 4

TABLE 1.—SUSPECTED AGE OF ONSET IN 26 PATIENTS WITH RHEUMATIC FEVER WHO ARE 5 YEARS OF AGE OR UNDER

| *Suspected Age of Onset* | *Number of Patients* |
|---|---|
| 5 years | 6 |
| 4 years | 9 |
| 3 years | 3 |
| 2 years | 5 |
| 1 year | 2 |
| Unknown | 1 |

TABLE 2.—SYMPTOMS AND SIGNS IN 26 CASES OF RHEUMATIC FEVER

| | | | |
|---|---|---|---|
| 1. Frequent U.R.I. | 12 | 9. Diastolic murmur at apex | 15 |
| 2. Fever | 24 | 10. Systolic aortic murmur | 5 |
| 3. Abdominal pain | 9 | 11. Aortic diastolic murmur | 6 |
| 4. Epistaxis | 5 | 12. Pericarditis | |
| 5. Joint symptoms | | Suspected | 3 |
| Subjective | 19 | Proven | 1 |
| Objective | 9 | 13. Enlargement | 15 |
| 6. Chorea | 1 (?) | 14. Left auricular enlargement | 9 (19) |
| 7. Skin manifestations | | 15. Congestive heart failure | 11 |
| Purpura | 1 | 16. Helpful EKG | 5 (21) |
| Erythema marginatum | 2 | 17. Sed. rate elevated | 17 (23) |
| Subcutaneous nodules | 1 | 18. Anemia | 11 (20) |
| 8. Systolic murmur at apex | 22 | | |

to indicate mitral valvular stenosis. Less than one-fourth of the children had aortic diastolic murmurs. The presence of aortic insufficiency, and, in particular, its development during the course of a suspected illness are strong evidence of rheumatic heart disease. Significant systolic murmurs at the aortic area were present or developed in 5 cases. Pericarditis was suspected because of precordial pain in 3 cases and was demonstrated by the presence of a pericardial friction rub in 1 instance. Definite cardiac enlargement demonstrated by physical examination and roentgenogram was noted in more cases and Q-T prolongation in 1. The sedimentation rate was rapid in 17 of 23 patients. It is to be remembered that the sedimentation rate may be normal in the presence of congestive heart failure, and, on the other hand, it may be elevated in a wide variety of conditions, and little stress should be placed upon this isolated finding. Anemia of 12 gm. or less was noted in 11 of 20 cases.

Although Dr. Duckett Jones has outlined adequate criteria for the recognition of rheumatic fever, many still require the presence of arthritis before establishing a diagnosis of rheumatic

myocarditis[8]. For example, in Case 8 the patient had congestive heart failure at age 2 with systolic and diastolic murmurs at the apex and pericarditis, but never had joint symptoms. Case 2, an autopsied case, the patient never experienced joint symptoms, the only evidence being that of myocarditis, fever, sedimentation rate. The recognition of rheumatic myocarditis is of utmost importance, otherwise murmurs in the younger age group may be attributed to congenital heart disease or endocardial fibrosis; furthermore, the opportunity for the early administration of cortisone or ACTH will be missed.

A number of patients had been thought to have congenital heart disease. The predominantly apical location of murmurs due to rheumatic disease as contrasted to the predominantly mid-sternal and basal location of murmurs in congenital disease should serve to differentiate the two. The presence of murmurs from birth suggests a congenital origin, but the details of examination at birth are frequently inadequate. Enlargement of the left atrium is of little help in differential diagnosis since it may be present with patent ductus arteriosus and in large hearts with long standing congestive heart failure. The development of aortic insufficiency during the course of an illness suspected to be rheumatic fever is important. There are congenital lesions with aortic systolic or diastolic murmurs, or both, such as coarctation of the aorta, aortic or subaortic stenosis, and the rare case of Eisenmenger's complex with aortic insufficiency. Pulmonary diastolic murmurs in such lesions as pulmonic stenosis or interatrial septal defect may at times be confusing. Furthermore, rheumatic fever may occur in children with congenital lesions, particularly interatrial septal defect. Here there may be acquired mitral stenosis with interatrial septal defect (Lutembacher syndrome). One must not confuse the dilated pulmonary arteries due to pulmonary hypertension in mitral stenosis or the occasional intrinsic pulsations of the pulmonary arteries in the presence of anxiety with the findings so commonly observed with interatrial septal defect. Occasionally the murmur of mitral insufficiency may be widely transmitted over the precordium and may simulate that due to interventricular septal defect. A mid-diastolic rumble at the apex is not infrequent in the presence of patent ductus arteriosus, and some have reported its occurrence with high ventricular septal defect.

Even more confusing than congenital lesions in the recognition of acute rheumatic fever in the early years of life is endocardial fibrosis, and the two conditions may have many features in common. Endocardial fibrosis is characterized by endocardial thickening and at times is accompanied by atresia or stenosis of the valves. There may be identical types of murmurs in both diseases. Craig reported 43 autopsied cases of endocardial fibrosis and about one-half had significant murmurs[2]. Stenosis of the aortic, mitral, pulmonic, and tricuspid valves was not uncommon and occurred in one or more valves in 25 of his cases. Blumberg in an unpublished series of 25 cases of endocardial fibrosis noted murmurs in about one-third of cases, and 6 of 25 had stenosis of either the aortic or mitral valves[1]. The electrocardiogram may show P-R prolongation in both diseases. Both may be subject to abnormal rhythms and we have seen 2 cases of endocardial fibrosis with auricular fibrillation. In both there may be a susceptibility to respiratory infections with exacerbation of symptoms

of congestive failure attending such infections.

The difficulties in differentiating endocardial fibrosis from rheumatic carditis are exemplified by the following case report.

J.B., male, age 5, was found to have a heart murmur at the age of 1½ when operated upon for an inguinal hernia. At the age of 3 he developed tonsillitis, aching in the legs, cough, and congestive heart failure. These symptoms persisted for 6 months, necessitating hospitalization on May 14, 1949. In September, 1949, he was seen at the Johns Hopkins Hospital where a diagnosis of coarctation of the aorta was made. Dr. Helen Taussig felt that there was also a lesion of the mitral valve because of loud systolic and diastolic murmurs at the apex. There was some question as to whether these were due to rheumatic fever or to a congenital defect. The coarctation was resected by Dr. Alfred Blalock on September 30, 1949. The patient temporarily improved but was subsequently admitted to Emory University Hospital on September 7, 1950, with auricular fibrillation and signs and symptoms of severe congestive heart failure. The heart was markedly enlarged, and there was a grade 4 systolic murmur at the apex with a low-pitched diastolic rumble. Roentgenograms and fluoroscopy showed generalized enlargement with a huge left atrium (Fig. 1). There was no anemia and the leukocyte count was 12,450 with a normal differential. The sedimentation rate was 10 mm. in 1 hour. The clinical picture appeared quite typical of rheumatic fever with pancarditis. The congestive heart failure progressed, and the patient died suddenly March 2, 1951.

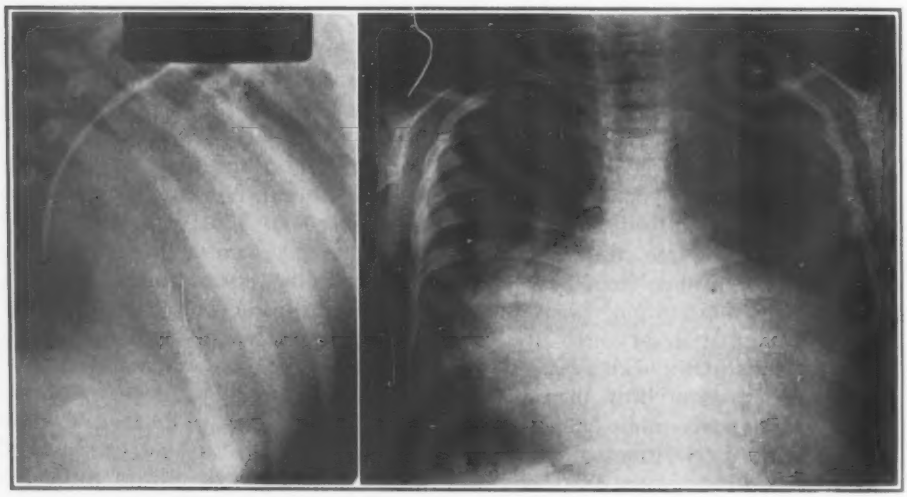

FIG. 1.—Roentgenograms of 5-year old male (J. B.), showing generalized cardiac enlargement with a huge left atrium.

Pathologic examination revealed the heart to weigh 310 gm. (average normal, 106 gm.). All chambers were greatly dilated, the left atrium extending to the right beyond the border of the right atrium. The endocardium of all chambers was involved by areas of opacity and thickening. The chordae tendinae were shortened and thickened. The mitral ring was greatly dilated. There were small nodules on the mitral valve leaflets. Microscopic examination showed no evidence of inflammatory lesions and no Aschoff bodies. There were marked thickening and proliferation of loose connective tissue both in the endocardium of the walls and on

the valve leaflets, and there was an increase in the amount of elastic tissue. There was no evidence of rheumatic lesions.

After a study of our data and the reports of Craig[2] and Blumberg[1] we would like to suggest the following points in differentiation of rheumatic myocarditis and endocardial fibrosis:

1) If no murmurs are heard in the presence of congestive heart failure, endocardial fibrosis is suggested rather than rheumatic fever.

2) A long-time survival after the onset of congestive heart failure favors rheumatic infection, since the majority of patients with endocardial fibrosis die within a year after heart failure ensues.

3) The presence of pericarditis rules out endocardial fibrosis and offers strong corroborative evidence of rheumatic fever.

4) The development of aortic insufficiency later during the course of the disease favors rheumatic fever.

5) Other stigmata of rheumatic infection such as chorea, subcutaneous nodules, erythema marginatum, and objective evidence of polyarthritis indicate rheumatic fever.

6) An abnormally rapid sedimentation rate without other cause in the presence of findings of rheumatic heart disease favors rheumatic fever.

7) Evidence of cardiac dilatation and congestive heart failure during the first 6 months of life without explanation by the presence of usual congenital defects suggests endocardial fibrosis.

8) The presence of coarctation with a large heart and congestive failure in the young age group suggests endocardial fibrosis. We have seen 3 patients with this association and Blumberg noted 2 cases in his series, whereas Craig noted 1 in his group. The presence of coarctation of the aorta, bicuspid aortic valves, and endocardial fibrosis would suggest that there is more than a casual relationship between the two conditions.

Fiedler's myocarditis, an unusual lesion in childhood, will not commonly cause confusion with rheumatic fever, since murmurs are inconspicuous. The findings of an enlarged heart and congestive heart failure in the absence of murmurs is more likely to be endocardial fibrosis in this age group.

On rare occasions Still's disease, sickle cell anemia, Schönlein's purpura, poliomyelitis, osteomyelitis, and Von Gierke's disease may cause confusion.

The possible value of ACTH and cortisone in the treatment of acute rheumatic fever demands its early recognition. An attempt has been made to offer some clinical data that are useful in early recognition.

**Summary.** Twenty-six cases of rheumatic fever occurring at age 5 or earlier are presented. Autopsies were performed on 4 and the diagnosis was established in the remaining cases by the presence of characteristic features of rheumatic infection or the development of rheumatic heart disease after a long term follow-up. The predominant manifestation was that of myocarditis or valvular lesions. Joint symptoms occurred in 19 patients, but objective signs were present in only 9. Findings of value in differentiating rheumatic fever and rheumatic heart disease from endocardial fibrosis are presented.

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# THE USE OF A CATION EXCHANGE RESIN IN THE MANAGEMENT OF THE FLUID RETENTIONS OF NORMAL AND TOXEMIC PREGNANCIES: FURTHER OBSERVATIONS

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In a previous report[3] we described the use of a cation exchange resin in the management of fluid retention in normal and toxemic pregnancy. Since the patients in this first series were hospitalized and were on carefully controlled dietary intakes of sodium, it seemed necessary to study the problem in outpatients, in order to determine how great a part the hospital diet had played in the response, and to what extent the resin could be used safely without laboratory control. In addition it seemed advisable to include in the second series several patients with abnormalities other than fluid retention.

**Material.** For this study, 26 pregnant women from 18 to 36 years were selected, solely on clinical evidence of the presence of edema. Eight were primagravidae; the remainder multiparae. In half of the patients we first observed edema between the 20th and 32nd week of pregnancy; in the other half, between the 33rd and 38th week. Of the 26 patients, 22 were clinic patients. All but 1 received the resin as outpatients, although 7 of them were subsequently admitted to the hospital for observation, or for treatment of their edema, or of other conditions.

**Method.** In this study (as in the preliminary one) the potassium and ammonium form of a cross-linked polyacrylic, polycarboxylic cation exchange resin† was used. Each patient was supplied with enough resin to last 7 days, at the usual dosage of 15 grams of the resin 3 times a day. Each was told of the need for resin therapy and of the importance of restricting her use of salt and salty foods; and each was advised to take the resin with meals, or dispersed in grapefruit juice, pineapple juice, or cola beverages. During each visit, their blood pressure, weight, and the presence or absence of clinical edema were determined.

**Results.** Acceptance. Of the 26 patients to whom the resin was supplied, 7 objected to taking more than a few doses. Five of these maintained that they had vomited every, or almost every dose; a 6th "just did not like the taste" of the resin. One, an extremely indifferent patient, vomited the first few doses of the resin, stopped taking it, resumed taking it without vomiting, but again stopped taking it—this time for reasons that she could not, or would not, give. It should be pointed out that 1 of the 5 patients who consistently vomited had a hiatal hernia and that another could not tolerate any powdered medicine. An 8th patient, who vomited after taking the resin dispersed in water, tolerated it well in cola beverages and continued to take it.

Mobilization of Fluid. In 17 of the 19 women to whom it proved acceptable, Resodec succeeded in aiding the mobilization of edema fluid, as demonstrated by rapid loss in weight and/or by the reduction or disappearance of edema. One of the 2 patients not in-

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† Resodec, trademark for product of Smith, Kline & French Laboratories.

cluded in the 17 took only 6 doses of the resin before the onset of labor and thereby provided us with some evidence of acceptance, but not of efficacy. The other, for reasons which we will discuss below, experienced no loss in weight nor in edema, although it appeared that she had tolerated the resin well and had taken it faithfuly.

In 8 of the 17 patients, fluid retention was eliminated by the resin-low sodium regimen. In 9, the regimen was only partially successful or was inconstant in its effect. The results recorded in Table 1 (describing A. M., a 29-year old nullipara, gravida, who, aside from an accumulation of fluid, was asymptomatic) are typical of those observed in the eight in whom edema was eliminated.

Two case histories will serve to illustrate the partial or inconstant success of the regimen in 9 of the 17 patients. The first describes the results achieved in a woman whose initial weight was high, the second, in a woman who appeared to have polyhydramnios:

R. L., a 32-year old para i, gravida ii whose usual weight was 195 pounds, developed an edema that was first detected in the 23rd week. The institution of Resodec therapy was followed by a profuse diuresis, and, as shown in Table 2, by a loss of 4¾ pounds in 3 days and a reduction of her edema. Because the continued administration of 45 grams of the resin a day had less pronounced effect on her residual, moderate edema, she was asked to take 75 grams of resin a day. (She tolerated this large dose well). After a week of this regimen, the mild edema persisting, the resin was discontinued. Within 1 week, her weight had increased by 6¼ pounds and her edema had become more pronounced. She then resumed taking Resodec, 60 grams a day. On this dose she gained only 3 pounds in 1 month and her edema was reduced. It would appear that Resodec produced a good initial response in this patient but that its repeat performance was not as successful.

S.B., a 21-year old nullipara, gravida i, whose usual weight was 109 pounds, was first seen 2/1/51, in the 28th week of her pregnancy. On 3/22/51, when it was found that her blood pressure was 130/95; her weight, 153¾ pounds; and her edema 3+, she was admitted to the hospital, where she remained until her delivery, 5/3/51. It was our clinical impression that she had pre-eclampsia. The serum protein, blood sugar, and

TABLE 1.—MOBILIZATION OF EDEMA IN PATIENT A. M.

| *Date (delivered 9/17/51)* | *Weight (usual weight, 130)* | *Blood Pressure* | *Edema* | *Resodec 15 gm. t.i.d.* |
|---|---|---|---|---|
| 2/16/51 | 128¾ | 100/65 | 0 | |
| 4/11/51 | 134¾ | 100/62 | 0 | |
| 5/3/51 | 140½ | 106/60 | 2+ | started |
| 5/10/51 | 138 | 106/64 | 0 | stopped |

TABLE 2.—MOBILIZATION OF FLUID IN PATIENT R. L.

| *Date* | *Weight* | *Blood Pressure* | *Edema* | ℞; *Remarks* |
|---|---|---|---|---|
| 1/9/51 | 198¼ | 118/74 | 0 | |
| 2/12/51 | 203¾ | 100/68 | 0 | |
| 3/19/51 | 205¼ | 100/68 | 0 | |
| 4/23/51 | 214½ | 100/68 | 1+ | Resodec started (45 g./day) |
| 4/26/51 | 210 | 114/64 | ± | Resodec increased to 60 g./day |
| 5/3/51 | 209 | 110/70 | ± | Resodec increased to 75 g./day |
| 5/10/51 | 210 | 110/60 | ± | Resodec stopped |
| 5/17/51 | 216¼ | 98/60 | 1+ | Resodec resumed, 60 g./day |
| 5/31/51 | 218¾ | 100/50 | 1+ | |
| 6/7/51 | 219¼ | 110/70 | ± | Resodec stopped |

urea nitrogen values were within normal limits, as were hemoglobin and quantitative urine protein values. Her eyegrounds were normal.

From 3/22/51 until 4/13/51 she was placed on a low sodium diet and was sedated. Yet at the latter date her 3+ edema persisted and she had gained 5 pounds more. The improvement during the next week was slight, perhaps because she was probably ingesting extra sodium. At that time, her abdomen was 90 cm., in circumference at the umbilicus and 45 cm., in height. The uterus was extremely tense. The fetal rate was 150/min.; the position of the fetus was occiput left transverse. Her eyegrounds now revealed arterial attenuation and her blood pressure was 145/95.

Because of the size and tenseness of the uterus, a diagnosis of polyhydramnios was made. She was then given Resodec. In 1 day, as shown in Figure 1, she lost 5½ pounds; in 6 days her edema was reduced from 2+ to ±. In that same period she voided 25,200 cc. of urine while imbibing 19,950 cc. of fluids; whereas in the period between 4/13 and 4/21 she had voided only 16,500 cc. of urine while imbibing 17,520 cc. of fluid. In Figure 1, the circumference of the abdomen plotted against time suggests that the administration of the resin was followed by a mobilization of excess amniotic fluid. On May 3, she delivered a normal female of 7 pounds 14 ounces.

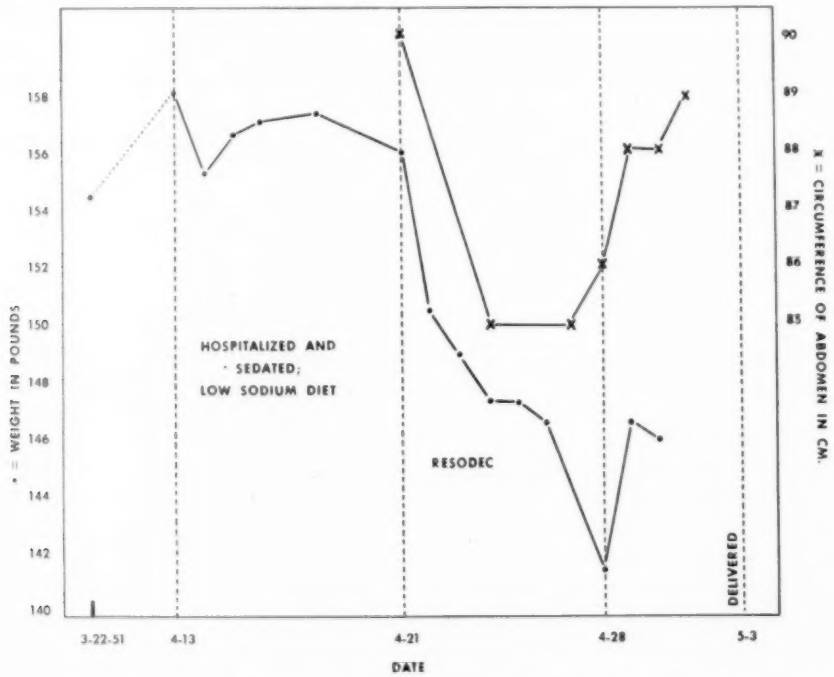


FIG. 1. Circumference of abdomen at umbilicus (x) and weight (•) of patient, S. B., before, during and after resin therapy.

PRE-ECLAMPSIA. In 2 of the 8 patients in whom the regimen of resin and salt restriction eliminated edema, pre-eclampsia developed. The report of one of these patients will illustrate this:

D.M., a 22-year old para i, gravida ii, whose usual weight was 158 pounds, was first seen 11/7/50 in the 17th week of her pregnancy. At that time, as is shown in Table 3, she weighed 160½ pounds, her blood pressure was 115/76, and there was no edema. 19 weeks later, on her visit, she

had gained 27¼ pounds over her usual weight and showed an edema of 3+. One week later, because she had not responded satisfactorily to 9 grams of ammonium chloride a day, she was supplied with Resodec. After 6 days her weight had been reduced and her edema had disappeared. However, because of the height of her blood pressure she was admitted to the hospital, where in 4 days, without Resodec, she responded well to bed rest, sedation and a low-sodium diet.

Three days after discharge (and 15 days before expected delivery) she was again edematous. Consequently, Resodec was restarted, again with complete mobilization of the edema. A sharp rebound in weight again occurred when Resodec was stopped. pounds and that her edema had disappeared. Within a week the edema and weight had returned. Again Resodec produced the same prompt loss of weight and edema. When 3 days later she had regained 5 pounds, she was hospitalized for a pre-delivery rest and her weight was stabilized by means of this rest and a low-sodium diet. The details of her essentially uneventful delivery 3 days later and of her postpartum course are not germane to this study.

**Discussion.** ACCEPTANCE. Since most pregnant women who have gained excessive weight because of the accumulation of fluid are almost completely

TABLE 3.—DEVELOPMENT OF PRE-ECLAMPSIA IN PATIENT D. M. DESPITE MOBILIZATION OF FLUID

| *Date* | *Weight* | *Blood Pressure* | *Edema* | ℞; *Remarks* |
|---|---|---|---|---|
| 11/7/50 | 160½ | 115/76 | 0 | |
| 2/13/51 | 174 | 120/70 | 0 | |
| 3/27/51 | 185¼ | 114/80 | 3+ | $NH_4Cl$, 9 g./day |
| 3/30/51 | 184¼ | 106/76 | 1+ | stopped $NH_4Cl$; started Resodec |
| 4/5/51 | 180 | 140/110 | 0 | hospitalized; bed rest, sedation, low Na; stopped Resodec; 230 mg. protein in 24-hr. urine sample |
| 4/9/51 | 178 | 100/60 | 0 | discharged |
| 4/12/51 | 185¾ | 90/50 | 1+ | Resodec re-started |
| 4/19/51 | 185¾ | 116/94 | 0 | Resodec stopped |
| 4/26/51 | 189 | 120/94 | 0 | |
| 5/1/51 | delivered | 170/108 | | |

RHEUMATIC HEART DISEASE. As a means of eliminating an accumulation of excessive fluid in a patient with rheumatic heart disease, Resodec proved adequate in the one patient of this type encountered in this series.

B.J., a 21-year old nullipara gravida i, was first seen on 11/14/50 in the 15th week of her pregnancy. Her medical history included rheumatic fever at the age of 12 and a relapse at 13. She was examined by Dr. George Mark, obstetric cardiologist at Temple University Hospital, who diagnosed aortic insufficiency and mitral insufficiency and who advised that she be kept at 'dry weight' throughout her pregnancy. On 4/12/51, as shown in Table 3, she had moderate edema. Resodec was then started, but was discontinued a week later when it was found that she had lost more than 8

asymptomatic and are thus unaware of any abnormality, it is frequently difficult to convince them that they should reduce their use of salt to a point where their food becomes unpalatable. Moreover, even with those patients who faithfully refrain from using salt, sodium has a way of insinuating itself into their diets. Therefore, if the ingestion of a resin substance will permit the patient to enjoy a more palatable and a more practically attained diet, a more satisfactory mobilization of the excess fluid may be accomplished.

Of course, if the resin proves disagreeable to the patient, that is another matter. However, if the accept-

ability of the resin is compared with that of other diuretic aids, such as the uncoated ammonium chloride tablets commonly used to control edema in pregnant outpatients, one finds that the resin, although less palatable, does not produce as many irritating side effects. It is my opinion, therefore, that of the 3 methods available to the obstetrician —diuresis, rigid sodium restriction, or Resodec therapy with moderate sodium restriction—the last mentioned is the most practical in the control of edema.

TABLE 4.—USE OF RESIN IN RHEUMATIC HEART DISEASE IN PATIENT B. J.

| *Date* | *Weight (usual 119 lbs.)* | *Blood Pressure* | *Edema* | *Rx; Remarks* |
|---|---|---|---|---|
| 4/12/51 | 128 | 140/30 | 1+ | Resodec; valid heart lesion |
| 4/19/51 | 119½ | 128/30 | 0 | Stopped Resodec |
| 4/26/51 | 130 | 140/30 | 1+ | Hospitalized; Resodec |
| 5/4/51 | 122 | 135/30 | 0 | Stopped Resodec |
| 5/7/51 | 127¼ | 128/38 | 0 | Restricted to 2 g. Na. |
| 5/14/51 | 125 | 130/30 | 0 | |
| 5/17/51 | onset of labor | | | |

Mobilization of Fluid. We have mentioned that the resin failed to stabilize the weight or reduce the edema of 1 of the patients and that it was only partially successful in 9 others. Although we have no quantitative data to explain these failures, it is likely that they occurred when the sodium ingested exceeded the capacity of the resin to adsorb it. In our previous study[3], 2 edematous patients who were permitted to ingest 6 to 9 grams of sodium a day while taking the resin lost no weight. Odell, *et al.*[2], using a resin similar to the one used by us, found that one patient (who, while on the resin and on a hospital diet including 1 gram of salt, had lost 10 pounds in 5 days) gained 17 pounds in the next 13 days as an outpatient. This 'failure', and ours, would be expected since the *in vivo* capacity in humans of the resin used in this study has been found by Hay and Wood[1] to be approximately 5 mEq./gram of resin, or about 5 grams of cations per daily dose of 45 grams. Since both sodium and potassium compete for positions on the resin lattice, actually this figure means that 45 grams of the resin will adsorb about 2 to 2.5 grams of sodium. Therefore, an edematous patient will lose weight and edema if she restricts her intake of sodium to a quantity not much greater than the capacity of the resin.

From our one case of polyhydramnios (S.B.), little can be concluded, except that future work should be done to determine if the resin can actually mobilize edematous fluid which is compartmented. That this should prove true might be suggested by the studies of Vosburgh, *et al.*[4], who showed that 1/3 of the water of the amniotic fluid is replaced every hour by water from maternal plasma.

Pre-Eclampsia. From our experience with patients C. D. and D. M. it seems evident that resin therapy does not prevent the development of pre-eclampsia, despite the fact that it does cause the disappearance of clinical edema. It may, however, be useful as adjunctive therapy in mild pre-eclampsia if fluid retention is an important part of the syndrome.

Safety. No clinical evidence of sodium or potassium deficiency nor of acidosis was seen, despite the fact that

the patients were not hospitalized nor followed by laboratory tests.

**Summary**. As a sequel to its administration to hospitalized patients, Resodec was given to 26 pregnant outpatients with edema.

1. Of these 26:
   a. Eight, because they objected to it or because they delivered soon after the first dose, did not take it long enough to provide data of significance.
   b. Eight realized complete disappearance of edema, accompanied by a substantial loss in weight.
   c. Nine realized a reduction in edema and in weight.
   d. One showed no improvement.
2. The resin therapy proved especially valuable in keeping a patient with severe rheumatic heart disease at 'dry weight'; it did not prevent the development of pre-eclampsia; it appeared to mobilize excessive amniotic fluid; it proved safe.

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# EVALUATION OF THE EFFECTS OF KHELLIN ON THE HUMAN ELECTROCARDIOGRAM

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and

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The introduction of every new drug or the new application of an old drug raises the question, "Is this an effective agent and how toxic is it?" Khellin or Ammi Visnaga is an old drug to the Egyptians who have used it for the relief of renal colic for many years[3]. In 1945 an Egyptian technician, who was using it prophylactically to prevent renal colic, noted that the angina pectoris from which he suffered also, was mitigated when he took the drug but

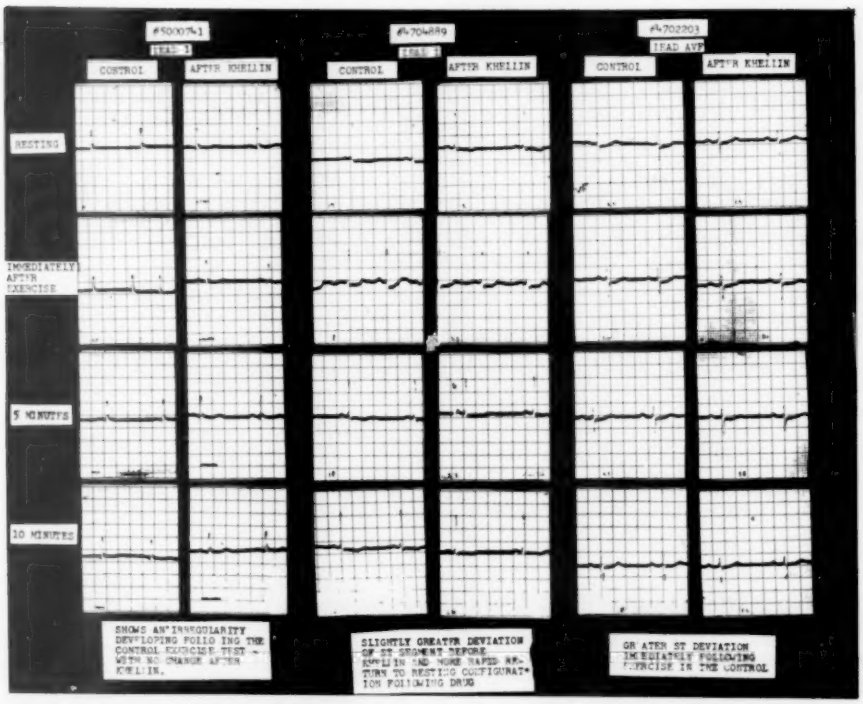
CONTROL
AFTER KHELLIN
CONTROL
AFTER KHELLIN
CONTROL
AFTER KHELLIN
LEAD I
LEAD I
LEAD AVF
RESTING
IMMEDIATELY AFTER EXERCISE
5 MINUTES
10 MINUTES
SHOWS AN IRREGULARITY DEVELOPING FOLLOWING THE CONTROL EXERCISE TEST — WITH NO CHANGE AFTER KHELLIN.
SLIGHTLY GREATER DEVIATION OF ST SEGMENT BEFORE KHELLIN AND MORE RAPID RETURN TO RESTING CONFIGURATION FOLLOWING DRUG
GREATER ST DEVIATION IMMEDIATELY FOLLOWING EXERCISE IN THE CONTROL

Fig. 1. Electrocardiograms in 3 cases following exercise without Khellin (control) and after Khellin.

A—Lead I. Shows an irregularity developing following the control exercise tolerance test. No change after Khellin.

B—Lead I. Slightly greater deviation of ST segment before Khellin and more rapid return to resting configuration following drug.

C—Lead AVF. Greater ST deviation immediately following exercise in the control.

returned when he temporarily gave up its use. Since that time, there have been many physiological and clinical reports on the drug. The first clinical reports came from Egypt and were followed by others from England[1,2,5,8] and the United States[4,7,11].

of amyl nitrate, but much more prolonged. Except with very large doses there is no effect on the pulse rate, respiration, bleeding or clotting times. The drug, when given intramuscularly is absorbed rapidly, reaching therapeutic levels in from 5 to 7 minutes.

TABLE 1.

Leads in which Major Changes Took Place and the Type of Change

| | |
|---|---|
| #4704485 | Control ST of Lead III depressed more than after Khellin.<br>Control pulse 98; after Khellin pulse 85. |
| #4804778 | Control Lead I negative T became diphasic, was isoelectric after Khellin.<br>Control pulse 103; after Khellin Pulse 85. |
| #5004613 | Control TV4 became diphasic; no change after Khellin.<br>Control Pulse 67; pulse after Khellin 67. |
| #4903161 | Control STV4 depressed; after Khellin STV4 elevated.<br>Control pulse 104; after Khellin pulse 79. |
| #4300035 | Control TV4 upright to inverted at 10 minutes; at same time after Khellin TV4 0.1 mm. less inverted. |
| #3702722 | Test positive diphasic to upright TI; same control and after Khellin.<br>Control pulse 84; after Khellin pulse 85. |
| #4905157 | Negative control, pulse 85; negative test after Khellin, pulse 75. |
| #4900909 | Control positive, with multifocal V.P.C.* STV4 depressed 1 mm.; after Khellin no irregularity, STV4 depressed 0.5, Control pulse 60; after Khellin, 60. |
| #5001338 | Control V4T diphasic to upright; after Khellin no change.<br>Control pulse 75; after Khellin, pulse 65. |
| #4602536 | Control ST2 depressed; TaVL lower. After Khellin, less marked ST and T changes.<br>Control pulse 63. After Khellin, pulse 57. |
| #5000741 | Control irregular after exercise. After Khellin, no irregularity.<br>Control pulse 75; after Khellin, pulse 60. |
| #4704889 | Control STI depressed 1 mm.; after Khellin ST2 depressed 0.5 mm.<br>Control pulse 60; after Khellin, pulse 53. |
| #4702203 | Control ST AVF depressed 1 mm. After Khellin ST AVF depressed 0.25 mm.<br>Control pulse 62; after Khellin, pulse 62. |

* V.P.C.—Ventricular premature contractions.

Khellin (Dimethyoxy–methyl–furan chromone) is one of the three crystalline substances of the fruit of the Ammi Visnaga, a plant indigenous to the Eastern Mediterranean countries. Its therapeutic effect is due to its direct relaxing action on smooth muscle which is especially great on the smooth muscle of the coronary arteries. Its dilating effect is said to be less than that

**Method of Study.** Ambulatory patients followed from 1 to 5 years in the cardiac clinic, who had a definite anginal syndrome which responded to nitroglycerine, were selected. Electrocardiograms were taken according to the technique of the Master two step test. The number of trips over the standard steps were calculated for age and weight; electrocardiographs at basal conditions of blood pressure and pulse were taken before the trips were made, immediately after exercise, at 5 minutes and again at 10 minutes. This

technique was followed both in control test and after the drug had been given. Following a control electrocardiogram the patient received 100 mg. of Khellin intramuscularly and remained at rest for ½ hour at which time the test was repeated. The criteria of Master were used in evaluating the results, that is, 1. depression of RS-T segment below the iso-electric line (PR level) of more than 0.5 mm. in leads 1, 2, or 4. A change from upright T wave to an iso-electric or inverted T wave (or change in T wave in opposite direction). 3. Presence of arrhythmia immediately after exercise which reverts to normal (for example, A. V. block).

**Results.** Thirteen cases were used in the study (Table 1, Fig. 1 and 2). A control exercise tolerance test and another ½ hour after the intramuscular injection of 100 mg. of Khellin were made. Limb, AV-R-L-F and V4 leads were taken in all cases. One case showed negative results before and after the drug. Three were positive in the control and negative after Khellin; 1 was positive to the same degree before and after Khellin; 8 were positive in the control and positive, but to a lesser degree, after the drug. In no case was the tracing after the use of the drug more positive than that of the control. In the cases that showed the most positive test in the controls and improved the most after Khellin, there was a slowing of the heart rate from 15-25

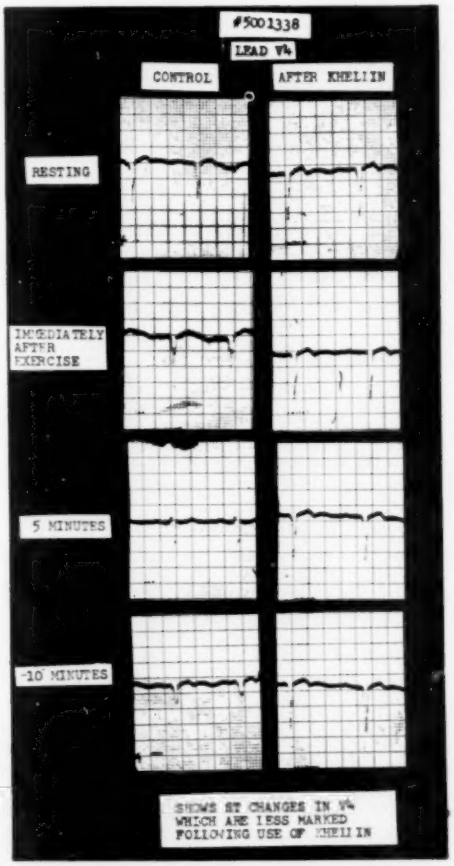


FIG. 2. Lead V4. ST changes less marked following use of Khellin.

beats per minute when the second tracing immediately after exercise was compared with the control record also taken immediately after exercise. No toxicity was observed after the intramuscular use of the drug. Several patients claimed subjective improvement of their angina for from 24 to 72 hours following the drug. Two patients who, because of pain, were unable to complete the calculated number of trips over the Master steps prior to the use of the drug, were able to do so ½ hour after it was injected.

**Conclusions.** Thirteen cases were tested by the Master 2 step test before and after the use of Khellin. The results show that the drug does have an effect on the electrocardiogram and that the records following the drug are nearer "normal" than the controls in 11 cases out of 13. No toxic reaction was observed in the dosage of 100 mg. given intramuscularly.

Khellin supplied in form of Ammivin, courtesy National Drug Co.
(Acknowledgement is made of the technical assistance of Mrs. Jenkins)

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# VENTRICULAR RATE RESPONSE FOLLOWING EXERCISE DURING AURICULAR FIBRILLATION AND AFTER CONVERSION TO NORMAL SINUS RHYTHM*

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Auricular fibrillation has been considered an asset rather than a liability in certain patients, because of the relative ease with which the ventricular rate in this arrhythmia may be slowed by digitalis[4]. The opinion has also been expressed that the conversion of auricular fibrillation to normal sinus rhythm does not significantly increase cardiac efficiency provided the ventricular rate during auricular fibrillation approximates the normal range[1,3,5]. The evidence supporting these views derives chiefly from observations on patients at rest. Accordingly it seemed advisable to study the ventricular rate response to exercise in patients with auricular fibrillation which was subsequently converted to normal sinus rhythm.

**Subjects and Methods.** Of the 10 patients studied, 4 had arteriosclerotic heart disease, 4 had rheumatic heart disease, 1 had hypertensive heart disease and 1 had no demonstrable heart disease. Seven patients were in congestive heart failure at the time of hospital admission. Cardiac compensation was restored by low sodium diet, mercurial diuretics and digitalis given to the point of therapeutic effect. Thereafter a maintenance dose of digitalis was given throughout the balance of the observation period. Four were given digitalis to the point of minor toxicity. Three patients who showed no signs of congestive heart failure were not digitalized. Auricular fibrillation was terminated in 9 of the 10 subjects by the use of quinidine. One reverted spontaneously.

Heart rates were recorded electrocardiographically. The subject was rested in the supine position until the ventricular rate was stabilized ("resting rate"). Exercise on the Master steps was then performed with the electrodes strapped in place. The number of trips over the steps and the speed of walking varied with each individual, but once established was kept constant for each subject throughout all subsequent tests. Following exercise the subject lay quietly in bed for the remainder of the observations. The heart rate was recorded immediately after exercise and at 1-minute intervals for the next 10 minutes. Exercise tests were performed on 3 consecutive days immediately before quinidine was given and on 3 consecutive days immediately after restoration of normal sinus rhythm.

**Results.** Rate responses in the individual patients in the 3 tests during fibrillation showed only minor variations and were similarly consistent during the 3 tests after normal sinus

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE 1.—VENTRICULAR RATE RESPONSE TO EXERCISE DURING AURICULAR FIBRILLATION AND AFTER CONVERSION TO NORMAL SINUS RHYTHM*

| Case | Rhythm | Rate at Rest | Rate Following Exercise: Immediate | 1 Min. | 2 Min. | 3 Min. | 4 Min. | 5 Min. | 10 Min. | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | A.F. | 88 | 135 | 122 | 117 | 110 | 108 | 100 | 100 | No demonstrable heart disease, no digitalis. 75 trips in 3 minutes. Quinidine. |
| Age 21 | N.S.R. | 68 | 107 | 98 | 90 | 82 | 80 | 80 | 80 | |
| 2 | A.F. | 90 | 153 | 120 | 100 | 100 | 98 | 102 | 90 | † AsHD. No digitalis. 20 trips in 1½ minutes. Quinidine. |
| Age 68 | N.S.R. | 72 | 103 | 87 | 80 | 75 | 75 | 75 | 72 | |
| 3 | A.F. | 88 | 160 | 110 | 107 | 103 | 102 | 103 | 98 | † AsHD. No digitalis. 25 trips in 1½ minutes. Quinidine. |
| Age 57 | N.S.R. | 75 | 115 | 100 | 95 | 85 | 85 | 85 | 80 | |
| 4 | A.F. | 105 | 175 | 138 | 128 | 128 | 123 | 123 | 123 | † AsHD. Digitalized. 50 trips in 3 minutes. Reverted spontaneously. |
| Age 55 | N.S.R. | 62 | 105 | 88 | 85 | 83 | 83 | 78 | 78 | |
| 5 | A.F. | 88 | 158 | 122 | 108 | 108 | 98 | 103 | 98 | † AsHD. Digitalized. 25 trips in 2 minutes. Quinidine. |
| Age 51 | N.S.R. | 82 | 118 | 108 | 102 | 98 | 93 | 92 | 90 | |
| 6 | A.F. | 77 | 168 | 125 | 107 | 98 | 95 | 93 | 88 | ‡ HHD. Digitalized. 25 trips ni 2 minutes. Quinidine. |
| Age 56 | N.S.R. | 74 | 122 | 105 | 94 | 88 | 85 | 82 | 80 | |
| 7 | A.F. | 95 | 133 | 113 | 105 | 100 | 100 | 100 | 95 | ** RHD. Digitalized to minor toxicity. 50 trips in 3 minutes. Quinidine. |
| Age 44 | N.S.R. | 88 | 115 | 103 | 97 | 93 | 90 | 93 | 90 | |
| 8 | A.F. | 88 | 185 | 180 | 140 | 122 | 117 | 112 | 108 | ** RHD. Digitalized to minor toxicity. 25 trips in 3 minutes. Quinidine. |
| Age 28 | N.S.R. | 92 | 145 | 137 | 125 | 115 | 113 | 109 | 98 | |
| 9 | A.F. | 63 | 168 | 102 | 82 | 82 | 73 | 80 | 68 | ** RHD. Digitalized to minor toxicity. 30 trips in 2 minutes. Quinidine. |
| Age 59 | N.S.R. | 57 | 95 | 76 | 66 | 63 | 60 | 60 | 60 | |
| 10 | A.F. | 100 | 165 | 143 | 125 | 128 | 117 | 118 | 115 | ** RHD. Digitalized to minor toxicity. 25 trips in 2 minutes. Quinidine. |
| Age 53 | N.S.R. | 88 | 131 | 116 | 112 | 109 | 100 | 97 | 90 | |

* Individual figures represent average of three exercise tests.
† Arteriosclerotic heart disease.
‡ Hypertensive heart disease.
** Rheumatic heart disease.

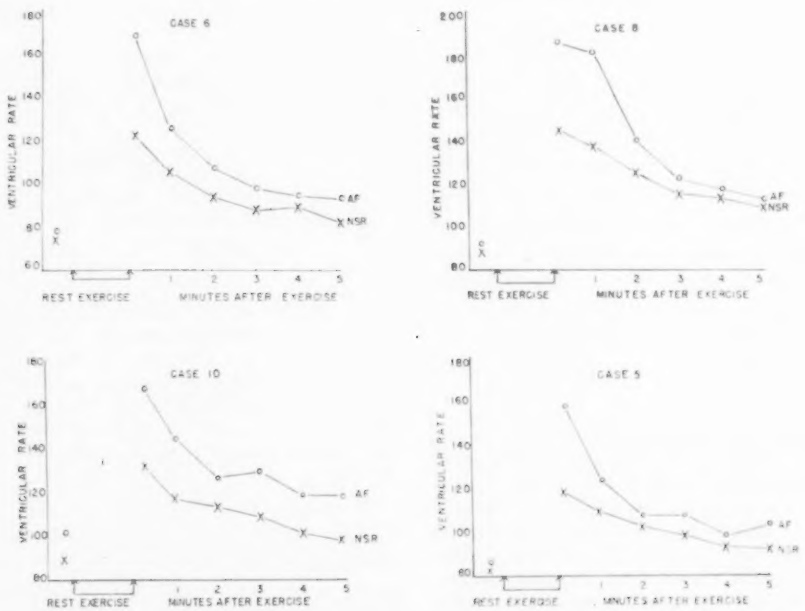


FIG. 1. Heart rate response to exercise. O—Auricular fibrillation. X—Normal sinus rhythm.
CASE 5. Arteriosclerotic heart disease. Digitalis. Exercise for two minutes.
CASE 6. Hypertensive heart disease. Digitalis. Exercise for two minutes.
CASE 8. Rheumatic heart disease. Digitalis to minor toxicity. Exercise for three minutes.
CASE 10. Rheumatic heart disease. Digitalis to minor toxicity. Exercise for two minutes.

rhythm had been established. In Table 1 the arithmetic averages of the rates for each subject during fibrillation are presented, together with the arithmetic averages of the rates with normal sinus rhythm.

Although the resting rate was lower after restoration of normal sinus rhythm in 9 of the 10 patients, in most instances this difference was not significant.

In all patients the peak ventricular rate response following exercise was significantly greater during auricular fibrillation than during normal sinus rhythm. Curves of averages in representative cases are shown in Figure 1. Digitalis given to 4 patients to the point of minor toxic symptoms did not prevent this exaggerated response to exercise in the fibrillating heart.

The rate of decline from peak levels was similar, though actual ventricular rates were slightly lower at all points on the curve during normal sinus rhythm.

**Discussion.** In 1924 Blumgart[2] showed that there was a greater rise in ventricular rate following a standard exercise test in patients with auricular fibrillation as compared to normal subjects and a delayed return to the previous resting level. Digitalis only partially prevented this exaggerated rate response. In 5 patients with fibrillation who did not receive digitalis the delayed return to the resting rate persisted after restoration to normal sinus rhythm. Examination of the data reveals that the peak ventricular rates following exercise were significantly higher in auricular fibrillation than after restoration to normal sinus rhythm.

The present study confirms these observations on the undigitalized patient. It further shows that in patients who have received digitalis even to the point of minor toxicity, the peak ventricular rate response after exercise is significantly higher during auricular fibrillation than it is after normal sinus rhythm is restored.

The peak ventricular rates occurring in patients with auricular fibrillation performing moderate work presumably would continue as long as the patient continued to work. Wolff[8] has shown that patients with mitral stenosis or limited cardiac reserve who develop paroxysmal rapid heart action manifest evidences of failure when the ventricular rate rises to 150 or more. Rates of such magnitude may be sufficient to impair diastolic filling of the ventricles. Furthermore, with such rapid rates in the presence of auricular fibrillation some ventricular contractions are so close to the preceding ones that they do not produce an effective stroke volume, and a pulse deficit results.

These phenomena diminish cardiac output and lead to the inefficient expenditure of energy. Cardiac catheterization studies by Hecht, Osher and Samuels[6] on 15 digitalized patients with auricular fibrillation showed that although the resting cardiac output changed little after restoration of noral sinus rhythm, the average output during exercise was significantly less during auricular fibrillation. Kory and Meneely[7] found no change in cardiac output following exercise in 2 patients without heart disease before and after conversion of auricular fibrillation to normal sinus rhythm, but in contrast demonstrated a striking increase in 6 patients with heart disease.

It would appear therefore that auricular fibrillation, even in the presence of cardiac compensation, adequate digitalis, and a controlled resting ventricular rate, has disadvantages which may be lessened by restoration to normal sinus rhythm.

**Summary.** The ventricular rate response following exercise was studied

in 10 patients during a period of auricular fibrillation and after restoration of normal sinus rhythm.

All showed an exaggerated ventricular peak rate response during fibrillation whether or not they had received digitalis.

All showed a significantly reduced ventricular peak rate response after restoration to normal sinus rhythm.

It is suggested that auricular fibrillation even in the presence of cardiac compensation, adequate digitalis and a controlled resting ventricular rate has disadvantages which may be lessened by restoration to normal sinus rhythm.

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## HYPERTENSION IN CHILDREN: A REVIEW

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THE isolated finding in children of persistent elevation of diastolic and systolic blood pressure without apparent cause is extremely rare. The occurrence of temporary or permanent hypertension as a complication of disease, however, is not uncommon in pediatric subjects. For this reason, it is of value to review the subject of hypertension in childhood. Our present knowledge does not permit an etiologic classification of hypertension, even though in a limited number of instances (unilateral renal disease and pheochromocytoma) this would appear to be possible. The subject can best be presented by describing, under the headings of the organ systems involved, the disease states in which hypertension is encountered. Where possible, points of etiologic and diagnostic significance will be emphasized.

It is important to recognize the difficulties of taking accurate blood pressure readings and the need for proper evaluation of the results obtained. A recent report of the committee of the American Heart Association reviews the details of technique[7]. In children, particular attention must be paid to the size of the arm cuff used[24]. The recommended width for adults is 12 cm.; for children under 8 years, 8 or 9 cm.; under 4 years, 5 or 6 cm.; under 1 year, 2½ cm.[7]. Diastolic readings taken at the point of cessation of sounds are more closely related to intra-arterial diastolic pressure than the change between the third and fourth phases[96]. Since resting blood pressure varies in children with age and weight[80], one cannot define a normal value for a child without reference to these factors. Information on this subject is well presented in the paper of Downing[25].

**Hypertension and Renal Disease.** Hypertension in children, in the great

majority of instances, is found in association with renal disease[43]. Acute glomerulonephritis is the commonest kidney disease of children, and the high incidence of hypertension in its course (60 to 70%) is well recognized. Although hypertension is usually only of temporary concern, it is of great significance because of its apparent relationship to the development of heart failure and encephalopathy[82]. The appearance of hypertension may precede the other manifestations of the disease, and severe renal impairment and cardiac failure can occur in the absence of hypertension[59]. The frequent association of loss of edema, disappearance of hypertension and abatement of the signs of renal disease is well known. Relationships between these various manifestations of glomerulonephritis are unclear.

The mechanisms responsible for the development of hypertension are as yet uncertain. Generalized vasospasm due to neurogenic hyperactivity has been assigned a major role on the basis of the observations of Pickering[72], and Arnott and Matthew[2]. Ferris, Reiser, Stead and Brust[30], however, failed to lower blood pressure during the hypertensive phase of acute nephritis by parenteral tetraethylammonium chloride. These authors concluded that neurogenic mechanisms did not appear to be of major significance in maintaining the elevated blood pressure. Hughes *et al.*[54] administered continuous caudal anesthesia to 5 children with hypertension and nephritis without significantly altering the hypertension or the course of the disease in 4 of the 5 patients. These results attest to the complexity of evaluating the etiologic role of so-called "neurogenic mechanisms," especially if based solely on the responses of patients to modification of neurogenic control of vasomotor activity.

The studies of Goldblatt *et al.*[37] have shown that a renal humoral mechanism may be responsible for hypertension developing after injury to the kidney. Renal ischemia, which can be produced by a number of experimental procedures, is presumed to cause the elaboration by the injured kidney of a substance (renin) which enters the blood stream and combines with a substrate (hypertensinogen) present in plasma to form an active pressor substance (angiotonin). This substance is enzymatically inactivated.

Other humoral pressor mechanisms have been demonstrated[90,91], but they will not be discussed here. It is tempting to assume that renal ischemia or anoxia is present in glomerulonephritis, and that this activates a humoral pressor system. Though increased amounts of renin have been found in the renal venous blood of a few patients with chronic glomerulonephritis[49], the significance of this or similar humoral mechanisms as a cause of hypertension in acute nephritis has not been established. Studies of renal hemodynamics by clearance techniques in patients with acute nephritis[9,26,27] demonstrate that hyperemia rather than ischemia is present. These findings in patients with nephritis do not lessen the likelihood that a humoral mechanism initiated by renal injury may be a major factor responsible for the hypertension occurring in this disease. The true nature of the alteration in renal circulatory hemodynamics that causes hypertension is not clear, and experimental renal hypertension can develop without evidence of renal ischemia as measured by clearance techniques[38].

Abnormalities in sodium and water metabolism as factors affecting blood pressure in nephritis are deserving of more study. Cardozo[17] has observed decreases in the blood volume of pa-

tients with acute nephritis following loss of edema and he feels that this points to the existence of hypervolemia during the stage of edema. This has long been suggested by clinical observations of increases in values for hemoglobin, hematocrit and serum protein concentrations after loss of edema. The frequent occurrence of loss of edema shortly before the disappearance of hypertension was pointed out by Roscoe[81]. Relationships between edema, renal damage, cardiac failure and hypertension are still unclear. The recognized effects of sodium and the salt active steroids on blood pressure emphasize the need for judicious attention to the salt balance of patients during the course of acute nephritis. The hypotensive effects of parenteral magnesium sulfate make it the vasodepressive drug of choice when hypertension becomes a major complication in acute nephritis[83,103]. This response is in all probability a non-specific effect related to the action of the magnesium ion on smooth muscle and its depressant effects on the central nervous system.

It is conceivable that hypertension in acute nephritis may under some circumstances be purposeful, acting to favor filtration through the inflamed glomerulus. In the authors' experience, significant decreases in the blood pressure of children with hypertension and nephritis have been obtained by parenteral administration of a potent new vasodepressor, C-5968, (Phthalazine-Ciba), but a decrease in renal function was associated with the temporary fall in blood pressure. The decrease in blood pressure produced by spinal anesthesia can also be associated with a depression of renal function, the degree of depression being related to the fall in blood pressure obtained[19]. It is thus apparent that measures which modify hypertension in acute nephritis should not be employed without regard to the effects of the lowering of blood pressure on renal function.

We have discussed acute glomerulonephritis as a distinct clinical entity. There are, however, a number of diseases in which glomerulonephritis occurs as a common and often serious complication and which deserve mention. Although the pathologic process responsible for the renal damage may differ from that underlying acute glomerulonephritis, the clinical course is often similar. Glomerulonephritis is one of the most serious complications of anaphylactoid purpura (Schönlein-Henoch syndrome)[35], and hypertension occurs in the majority of patients who have renal involvement. A raised blood pressure is sometimes found in the diseases of hypersensitivity, (sometimes loosely labeled the Collagen diseases), usually in association with signs of inflammatory renal disease. Its occurrence has been reported in periarteritis nodosa[10,23], and occasionally it is encountered in lupus erythematosus and dermatomyositis. Progressive renal disease and malignant hypertension have been reported in patients with scleroderma[85]. In some instances the onset of signs of nephritis may precede the other manifestations of the generalized disease. These conditions should be considered in the differential diagnosis of patients considered to have acute glomerulonephritis who demonstrate unusual findings or an atypical course.

Apart from acute nephritis, a raised blood pressure occurs in a variety of chronic renal diseases. In most instances in which a child is investigated for persistent hypertension, the ultimate diagnosis is that of chronic glomerulonephritis or chronic bilateral pyelonephritis. Other examples of bilateral renal disease which may be associated with hypertension are: polycystic kidneys[76], symmetrical cortical necrosis[15], the renal anoxic syndrome

(or "lower nephron nephrosis")[13,61,64]; thrombosis of the main renal vessels[106], and obstructive lesions of the urogenital tract[16].

Unilateral renal disease deserves special mention as a cause of persistent hypertension. This association has been reported in a number of conditions which include pyelonephritis, renal hypoplasia, abnormalities of the renal artery, renal tumors, calculi, hydronephrosis and hydroureter[8,16]. In many instances multiple lesions have been found.

The commonest unilateral disease would appear to be pyelonephritis, either alone or as a complication of other lesions. Of 32 cases followed for 1 year or longer in which nephrectomy resulted in relief of hypertension, 10 were children, and in 8 of these the underlying disease was chronic pyelonephritis[36].

The role of a diseased kidney in the production of hypertension was suggested by the results of nephrectomy[21,75] long before the relation of renal ischemia to hypertension was established by experimental data[37,102]. The latter work stimulated the publication of numerous reports of nephrectomy in patients with hypertension and unilateral renal disease who were benefited by the operation. In a recent review, however, it is apparent that operation is successful only in a minority of patients[94]. It is also worth emphasizing that a large number of patients with unilateral renal disease never develop hypertension. Thus, in a review of 500 children with pyelonephritis, Kimmel[56] selected 91 patients in whom adequate investigation had been carried out. Of these, 68 patients had unilateral disease and 23 bilateral disease. Hypertension was present in approximately 10% of each group.

From a therapeutic standpoint, a search for unilateral renal disease is of considerable importance in any child with persistent hypertension. Since one kidney is usually functioning normally, routine tests of renal function may be normal and it is essential to carry out thorough urologic studies on such patients.

The occurrence of hypertension with obstruction of the main renal artery by a variety of lesions has been reviewed by Yuile[106]. Most of the material quoted was obtained from postmortem reports, chiefly in adults. Examples in childhood are exceedingly rare. The most frequently mentioned case is that of a child who recovered from chronic hypertension after an ectopic kidney was removed. The renal artery was found to be obstructed by a plug of smooth muscle which was thought to be a congenital anomaly[58]. Platt[74] has recorded the details of a child with a congenital abnormality of the vascular supply. A functionless left kidney was supplied by 4 small renal arteries and there was no sign of a main arterial trunk. In addition, microscopy of the kidney showed evidence of congenital hypoplasia and chronic pyelonephritis, so that the hypertension could not be attributed solely to the abnormal blood supply. An aneurysm of the main renal artery was found in a child with persistent hypertension which improved following nephrectomy[53]. The removed kidney showed evidence of chronic glomerulonephritis, and since the patient had also been subjected to bilateral lumbar sympathectomy, the relation between the aneurysm and raised blood pressure was uncertain.

Renal infarction is known to cause hypertension in adults[1], but records of blood pressure changes are absent in most reports of infarction in children.

Hypertension is not uncommon in cases of Wilm's tumor (embryoma of the kidney)[22,55,73,93], and in some series has been present in over 50% of the

patients. Reduction of blood pressure to normal levels following operation has been observed[22,57,73]. Hypertension may be so severe as to be responsible for the presenting symptoms. A 3-year old child who died of hypertensive encephalopathy was found to have a Wilm's tumor at postmortem[55]. Elevation of blood pressure in association with Wilm's tumor may be a result of ischemia due to compression of renal tissue or to direct pressure on the blood vessels at the hilus of the kidney. A relationship of hypertension to raised intra-capsular pressure and ischemia is also suggested by the interesting report of a child with a large kidney abscess and hypertension which disappeared after nephrectomy[55]. The suggestion that in Wilm's tumor the neoplastic tissue itself might produce a pressor substance was made by Pincoffs and Bradley[73]. These authors reported a significant fall in blood pressure following nephrectomy in 2 patients and a recurrence of hypertension when metastases appeared; however, the possibility of compression of the remaining renal artery by local recurrence of growth was not excluded.

**Hypertension and Disease of the Endocrine Glands.** Certain endocrine disorders in children may be associated with a raised blood pressure. These include hyperthyroidism, disturbances of adrenal cortical function, pheochromocytoma and ovarian agenesis[101].

In children with hyperthyroidism, changes in the cardiovascular system occur at an early stage. Tachycardia is found in all cases. The hypertension is characterized by an elevation of systolic pressure, a normal diastolic and a large pulse pressure. These findings can be explained on the basis of increased cardiac output combined with peripheral vasodilatation. This systolic rise in blood pressure is clinically of little significance.

Pheochromocytoma as a cause of hypertension is often sought for but seldom found. We are here chiefly concerned with the mechanism of production of hypertension. These tumors have been shown to contain varying proportions of epinephrin and norepinephrin[5,41,52]. Intravenous injection of norepinephrin in physiologic amounts produces peripheral vasoconstriction, elevation of systolic and diastolic pressures, and reflex bradycardia without significant change in cardiac output. Epinephrin in equivalent doses results in an increase in cardiac output, tachycardia and peripheral vasodilatation. The latter serves to counteract the effect of increased cardiac output, so that diastolic blood pressure may even fall[40]. The variable clinical picture in patients with pheochromocytoma may represent different combinations of epinephrin and norepinephrin effects, although analysis of tumors removed at operation shows little correlation between the type and amount of pressor substance present and the clinical course[41]. It is not generally realized that the classical description of paroxysmal attacks of hypertension is by no means universal; thus, only 2 of 7 cases of pheochromocytoma in children had paroxysmal features[101]. The lack of fluctuation of blood pressure can render the diagnosis indistinguishable from essential hypertension[39,105], and there are examples in adults and children of unexplained or "essential" hypertension in which the presence of pheochromocytoma had not been excluded[20,77]. In view of the success of early operation the diagnosis should be made before the onset of complications such as heart failure or malignant hypertension. The procedures by which a diagnosis may be established have been fully dealt with by various authors[14,29,62,78,98,99]. It is worth mentioning that in some cases

2 tumors have been reported and both may be extra-adrenal[95]. Exploratory laparotomy should probably be considered in any child with otherwise unexplained persistent hypertension.

The occurrence of hypertension in disorders of adrenal cortical function in children is well recognized. It has been found in Cushing's syndrome, in the adrenogenital syndrome and with adrenal cortical tumors[101]. Desoxycorticosterone (DOCA) is known to have a pronounced effect on blood pressure both in man and animals[33,70]. The hypertensive effects of DOCA and salt given together to adults with Addison's disease was first reported by Loeb *et al.*[60]. Hypertension occurs in cases of DOCA overdosage[101]. The favorable effects of low salt intakes on the level of blood pressure in hypertensive disease is well known[86]. Hypertension is at times encountered during the course of administration of ACTH and cortisone, and pre-existing renal disease apparently predisposes a patient to such pressor effects[71]. The pressor effects of DOCA and "salt-active" adrenal steroids are closely related to the salt intake, being accentuated by supplementary salt, and diminished or absent when sodium is restricted[70]. Some evidence suggesting mechanisms whereby adrenal cortical activity influences blood pressure has been provided by experimental studies. Adrenalectomy lessens or abolishes experimental renal hypertension and prevents its development[11,38]. The administration of DOCA and supplemental salt hastens the development of renal hypertension and has been reported to lead to the production of hypertension and nephrosclerosis[33,88]. Since renal lesions and renal hypertrophy accompany the hypertension produced by the administration of DOCA and salt[11,34], it is obvious that the kidney participates in the production of this hormonal hypertension. The inter-relationships between vascular damage to the kidney, renal humoral pressor systems (renin-angiotonin and VEM-VDM), and abnormalities of adrenal cortical function in the production and maintenance of hypertension are complex[11,34,45,68]. It is clear that adrenal cortical function, particularly that mediated by the "salt-active" steroids, markedly influences blood pressure, and hypertension cannot be maintained in the absence of the adrenal glands. Disorders of the adrenal are uncommon in children and thus do not constitute a frequent cause of hypertension; nevertheless, the possibility that the adrenal cortex may participate in the pathogenesis of the commoner types of hypertension in childhood deserves more study.

A number of patients with the rare syndrome of ovarian agenesis also have hypertension. Of 20 cases mentioned by Wilkins[101] 9 had a raised blood pressure. The presence of coarctation of the aorta was demonstrated in 4 children. In the remaining 5 patients, the cause of the hypertension was undetermined.

**Hypertension and Disorders of the Central Nervous System.** Elevation of blood pressure has been found in patients with cerebral hemorrhage, infections of the central nervous system, following cerebral trauma and neurosurgical procedures and in association with raised intracranial tension.

In considering the genesis of hypertension of central origin, several factors have to be taken into account, and they can best be illustrated by reference to acute poliomyelitis. A rise of blood pressure is not uncommon in this disease and in one series was present in nearly 50% of patients[63]. In children it is usually only a temporary finding[46].

Most observers have noted that in both children and adults hypertension is most commonly associated with bul-

bar disease and respiratory difficulty [48,63,89]. Stimulation of autonomic nuclei in the hypothalamus and medulla of animals readily causes hypertension[12,100], and this suggests a possible mechanism in cases of poliomyelitis. Other factors which might be responsible for, or contribute to, a rise of blood pressure are anoxemia, accumulation of carbon dioxide, and the mechanical effects of artificial respiration. In normal persons, lack of oxygen or accumulation of carbon dioxide in the blood may have a pressor effect[44,47], and the relation of cerebral anoxia to hypertension has been established experimentally[66]. We are unaware of detailed studies on anoxemia and hypercapnea in patients with poliomyelitis. McDowell and Plum[63] made blood gas analyses in some patients with poliomyelitis and concluded that anoxemia and hypercapnea played little, if any, part in the production of hypertension.

That artificial respiration might directly influence blood pressure was suggested by these authors' experiences with 3 cases of the Guillain-Barré syndrome, in all of whom hypertension developed while the patients were in a respirator and promptly disappeared when they were removed from it. This sequence of events was not observed in their cases of poliomyelitis, in many of whom (mostly adults) there was a prolonged elevation of blood pressure which outlasted the period of artificial respiration. It is important to remember that the appearance of hypertension after the acute phase of the disease may be the result of renal damage produced either by renal infection or renal calcinosis, which are known to occur in patients who have spinal cord damage or who are immobilized for other reasons[32].

In recent years, a small group of children has been described with the unusual syndrome of paroxysmal hypertension, diminished lacrimation, excessive salivation and sweating with blotching of the skin[3,79]. In all of these patients, a diagnosis of pheochromocytoma could not be established, and their symptoms were attributed to a disturbance of the autonomic system of unknown etiology. They resembled in many respects the "hypertensive diencephalic syndrome" seen in patients with essential hypertension[67,87] and with organic disease of the thalamus[28,69].

In addition to organic disturbance of the central nervous system, a rise in blood pressure may occur in response to various external stimuli. Such a sequence of events has been demonstrated experimentally by the work of Medoff and Bongiovanni[65] in which hypertension in rats was produced by audiogenic seizures. There are many examples in humans of hypertension appearing after exposure to severe mental or physical stress[42,84,104].

In practice it is not uncommon to observe an elevated blood pressure in a patient who is emotionally disturbed, for example, during clinical examination. This is found in children as well as in adults and in most instances the hypertension, which is largely due to a systolic rise and is accompanied by tachycardia, subsides after a short period of rest. These transient episodes are usually considered to reflect vasomotor instability. There is some evidence to suggest that in adults such a pattern of reaction to mental and other stimuli may predispose to the development of essential hypertension in later life[50]. So far as we know, there have been no investigations which indicate that the same may be true of children.

**Hypertension and Cardiovascular Disease.** Disorders of the heart and great vessels, such as patent ductus arteriosus, aortic insufficiency and arterio-venous shunts, may be accom-

panied by hypertension. The elevation of blood pressure is primarily systolic, and diastolic pressure is usually normal or reduced. In these conditions, hypertension is the result of an increased cardiac output without increase in peripheral vascular resistance.

In some cases of patent ductus arteriosus it is not uncommon to observe a decrease in systolic pressure and pulse pressure following operation, even in those which were not originally considered hypertensive[18]. It may be of interest to note that acute episodes of hypertension have been observed during and shortly after operation[4].

Coarctation of the aorta is probably the commonest cause of hypertension in childhood other than renal disease, and it should be considered in every infant or child who has a persistent elevation of blood pressure without apparent cause. The diagnosis can readily be established on the basis of finding a raised blood pressure in the arms with normal or low blood pressure in the legs. The mechanism of the production of the hypertension was originally thought to be due solely to the mechanical effects of aortic constriction. Clinical and experimental evidence is, however, accumulating which does not allow this simple explanation. Renal, humoral and neurogenic factors have been implicated[48].

In conclusion, we should mention that there are other diseases in which hypertension may be found which do not fit into any of the previously mentioned categories. These include, acrodynia[6], lead poisoning[31] and sickle cell anemia[51], to mention a few.

In addition hypertension is sometimes observed in obese children. As in adults, overweight children may have higher than normal blood pressure readings[92,97] which return to normal after loss of weight. It may be difficult in these patients to be certain that the hypertension is not due, in part, to the thickness of the tissues under the blood pressure cuff.

**Summary.** The occurrence of temporary or permanent hypertension in association with other disease is not uncommon in children, though unexplained or essential hypertension is exceedingly rare. In the majority of instances, hypertension in children is associated with renal disease, the most frequent cause being acute or chronic glomerulonephritis. Chronic pyelonephritis alone or in combination with obstructive uropathy is also a common cause of hypertension in children and is of particular significance when only one kidney is involved. Though unilateral renal disease is not always associated with hypertension and relief of hypertension following nephectomy is obtained in a minority of such cases, it should be sought for as a cause of otherwise unexplained hypertension in children. Hypertension in children is occasionally encountered with diseases of the endocrine system, particularly pheochromocytoma and disorders of the adrenal cortex. It also can result from infection of, or damage to, the central nervous system, as well as from increased intracranial tension due to any cause. It may be found in some children with diseases of the heart or great vessels.

Care should be exercised in the selection of the proper cuff for blood pressure determinations in children. Elevation of systolic pressure and an associated tachycardia can be manifestations of apprehension in children in response to medical examination, and proper attention should be accorded these factors when the diagnosis of hypertension is made in children.

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GYNECOLOGY AND OBSTETRICS

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# DIABETES MELLITUS AND PREGNANCY

## WITH SPECIAL REFERENCE TO FETAL AND INFANTILE LOSS

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THE present review attempts to consider the significant contributions to the subject of diabetes mellitus and pregnancy that have appeared since the publication, in 1946, of Eastman's comprehensive review[10]. Although the pertinent interim literature to the end of 1948 has already been analyzed by Moss and Mulholland[38], many of the conclusions derived therefrom have been amplified or modified by the numerous additional contributions that have meanwhile been published. Most of the relevant papers have appeared in the American and British literature.

FREQUENCY. The association of diabetes and pregnancy is no longer the rare phenomenon that it was during the pre-insulin era. At the present time the frequency with which the disease is encountered among pregnant women is variously estimated at from 1 in 50 to 1 in 900, averaging about 1 in 500[3,10,13,16,45,52]. The latter figure approximates the estimated incidence of diabetes among all women of childbearing age[30]. This close coincidence would appear to confirm the view, generally held by clinicians, that there is no significant sterility among diabetic women under modern conditions[16].

Further evidence of the fact that diabetic pregnancy is no longer rare is the circumstance that clinical studies of more than 1800 such pregnancies have been published during the past 5 years. This aggregate greatly exceeds the number of cases reported in any similar earlier period. In Table 1 are listed only the largest and most detailed of the recent studies.

THE PREDIABETIC STATE AND PREGNANCY. The frequency with which gestational complications, fetal overdevelopment, fetal death, and loss of the newborn infant may complicate the pregnancies of women destined to become diabetic in middle age was emphasized by a number of authors prior to 1940. Their early observations have stimulated further inquiries into this subject since that time[2,12,13,17,20,26,32,34,36,38,41,42]. With one notable exception[20], all interim studies have confirmed that these phenomena are not uncommon among "prediabetic" women, at least during the 10 year period immediately preceding the onset of the disease. Opinion is more divided, however, as to whether the complications under consideration may be encountered in significant numbers during intervals

TABLE 1.—DIABETIC PREGNANCY

Clinical Studies of 1799 Pregnancies Reported During 5-year Period, 1947–51

| *Reporting Authors* | *Refer. No.* | *Hospital or Clinic* | *Period of Study* | *Pregnancies Studied* |
|---|---|---|---|---|
| *British:* | | | | |
| Peel and Oakley | 45 | Questionnaire, 26 hospitals. | 1942–49 | 458 |
| Peel and Oakley | 45 | Kings College Hosp., London. | 1942–49 | 141 |
| Gilbert and Dunlop | 13 | Simpson Memorial, Edinburgh. | 1943–47 | 70 |
| Barns and Morgans | 3 | Univ. College Hosp., London. | 1929–48 | 58 |
| *American:* | | | | |
| White | 61 | Joslin Clinic, Boston. | 1934–48 | 439 |
| Hall and Tillman | 16 | Sloane Maternity, N. Y. C. | 1924–50 | 147 |
| Given, Douglas & Tolstoi | 15 | Lying-in Hospital, N. Y. C. | 1930–48 | 131 |
| Reis, DeCosta & Allweiss | 49 | Michael Reese Hosp., Chicago. | 1935–49 | 92 |
| Patterson & Burnstein | 43 | Charity Hosp., New Orleans. | 1937–47 | 71 |
| Rike & Fawcett | 52 | Magee Hosp., Pittsburgh. | 1937–46 | 55 |
| Randall | 46 | Mayo Clinic, Rochester. | 1933–46 | 50 |
| Moss & Mulholland | 38 | U. of Virginia Hosp., Charlottesville. | 1929–48 | 48 |
| Palmer, Crampton & Barnes | 40 | Virginia Mason Hosp., Seattle. | 1944–47 | 39 |

TABLE 2.—DIABETIC PREGNANCY

Chief Clinical Features of Cases Reported During 5-year Period, 1947–51
(Viable Pregnancies Only)

| *Features* | *Combined Data* | |
|---|---|---|
| | *British Clinics* | *American Clinics* |
| Total pregnancies studied (No.): | 599 | 850 |
| Features of maternal diabetes (%): | | |
| Juvenile type | — | 46.3 |
| Established more than 10 years | 20.1 | 35.8 |
| Insulin therapy required | 86.8 | 88.0 |
| Complications of pregnancy (%): | | |
| Hydramnion | 27.7 | 7.3 |
| Vascular hypertension | — | 15.6 |
| Preeclamptic toxemia | 17.0 | 25.1 |
| Cesarean section rate (%): | 35.7 | 50.7 |
| Maternal mortality rate (%): | 2.0 | 0.7 |
| Infant mortality rate (%): | 36.7 | 19.1 |

Note the differences between the clinical material, complications and results, respectively, encountered in Great Britain on the one hand, and in American clinics on the other. Because of these differences, the data for the two countries have been considered separately in this and the following Tables. The number of pregnancies analysed in these Tables does not include all of the cases listed in Table 1. The available data with respect to some pregnancies were not complete enough for the purpose (Refs. 3, 13, 38, 43), and part of the data in other instances (Refs. 15, 16, 40, 49, 52) was concerned with nonviable pregnancies.

more distantly antedating the onset of the diabetes[2,17,34].

The finding of a resemblance in kind, and partly in frequency, between these complications and those encountered in diabetic pregnant women has been of great interest. It is apparent that hyperglycemia can hardly be an important factor in their causation[2]. Moreover, experimental proof that hyperglycemia may influence fetal development and wellbeing unfavorably is not uniformly obtainable when the question is examined in alloxan-treated[8,18,27,35,54] or depancreatized pregnant rats[50]. Consequently, the probable existence of some other factor prejudicial to fetal wellbeing in the pregnancies of prediabetic and diabetic women has been assumed, and interest has cen-

tered upon the likelihood that a dysfunction of the pituitary gland may be common to both types of patient. Thus, an overproduction of the anterior pituitary diabetogenic-growth factor of Young[63] has been postulated, particularly by British authors[2,3,12], and the question has been put to experimental test by injecting this hormone into pregnant rats. Although a high rate of fetal resorption and stillbirth can be provoked under these circumstances[4], the significance of such experimental findings must be interpreted with caution.

Effect of Pregnancy Upon Maternal Diabetes. Under modern medical management most diabetic women who become pregnant face little risk of fatal consequences. The maternal mortality in recently reported series of cases is not only low, but is attributable mainly to obstetric accidents occurring during the earlier years of these studies.

The undertaking of pregnancy by a diabetic woman may be said to be hazardous for her principally, and perhaps only, if her disease has been established for more than 25 years[59,61], or if its medical control has not been uniformly satisfactory. In the former instance, the woman is apt to be prematurely aged with respect to her cardiovascular system; she therefore faces a definite risk of vascular accidents during the course of pregnancy[9]. In both instances, she is vulnerable to the development of gestational toxemia. White[59] believes that where the disease has been established for a long period, the advisability of therapeutic termination of pregnancy must be seriously considered during the early months, unless rigid medical control is assured throughout the remainder of gestation.

As is well known, most pregnant women develop a moderate lowering of the renal threshold for glucose excretion at one time or another during the course of gestation. Associated with this there may be an unusual lability of blood-sugar levels, and a vulnerability to conditions which favor the development of keto-acidosis. Diabetic gravidas are not only subject to these physiologic phenomena, but many of them also develop some change of glucose-tolerance or insulin-requirement during the later months of gestation. The most frequently reported change is an increase of need for insulin[15,16,45]. Regardless of whether the insulin-requirement be increased or diminished, however, the change is usually temporary, inasmuch as a return to prepregnancy conditions ensues, generally very rapidly, during or following delivery[45]. It is reported that where delay is encountered, the prepartal change has most often been one of diminution[16].

Effect of Diabetes Upon Pregnancy. Diabetes in pregnant women predisposes to a higher than "normal" frequency of spontaneous early abortion[10,38,43,57], and to an increased incidence of late gestational toxemia (see below).

The principal impact of the disease, however, is to be seen in its evil effects upon the fetus during the late months of gestation. Fetal death *in utero* is both characteristic and frequent, and is associated with a high rate of early neonatal loss[45]. To these accidents must be added an increased frequency of intrapartal death or "fresh stillbirth", and a small late neonatal infant loss. The combined wastage at the present time is not as serious as it formerly was, but it still exceeds, by more than 5 times, the corresponding "standard" losses from stillbirth and neonatal infantile death met with in overall obstetric practice (see Table 2 *et seq.*). Because the fetus and infant thus suffer the brunt of the morbidity

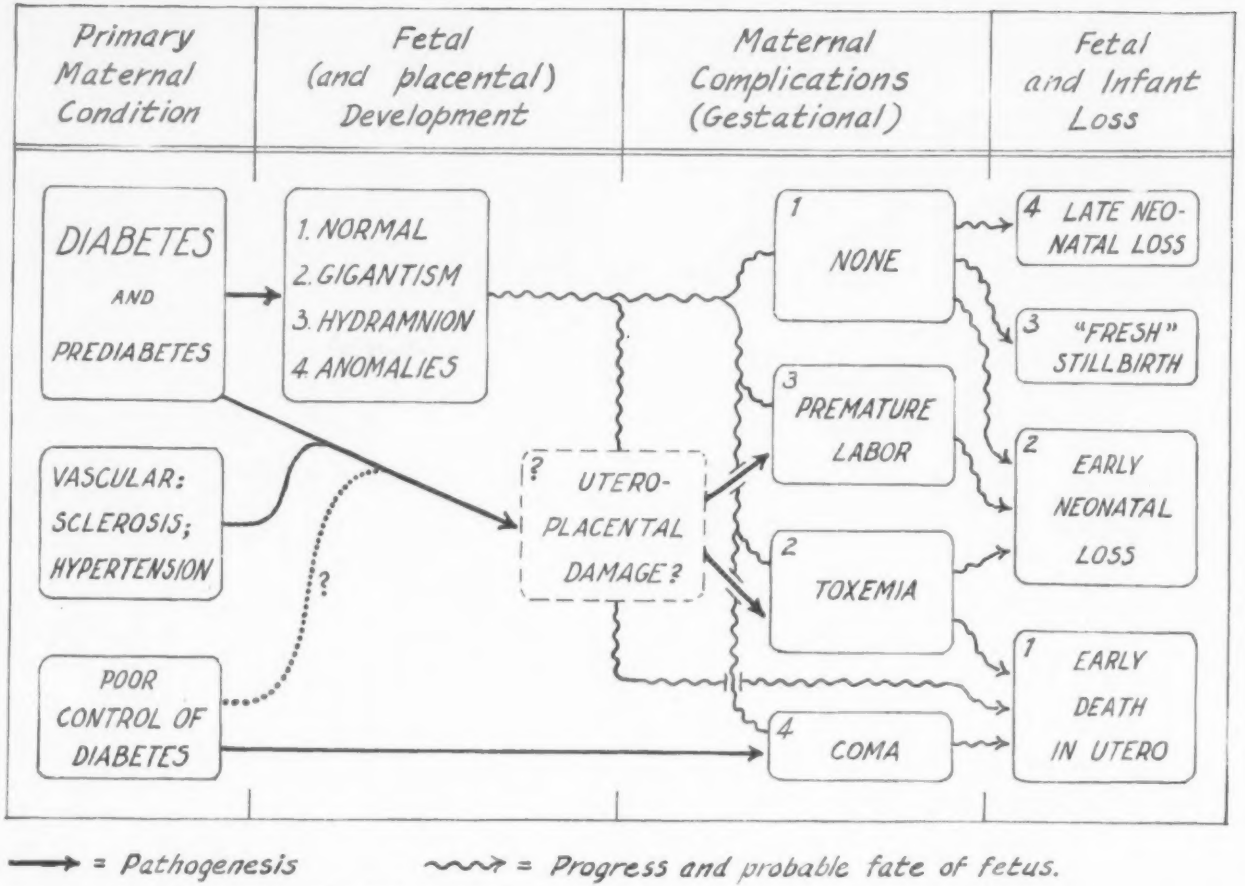


FIG. 1. DIABETIC PREGNANCY: Causes and Nature of Fetal Loss. The numerals indicate the order of frequency with which the conditions listed in each column are encountered.

associated with diabetic pregnancy, the factors responsible warrant special attention.

CAUSES AND NATURE OF FETAL AND INFANT LOSS. 1. *The Possible Factors.* Briefly listed, these include the primary maternal disease and such complications as toxemia and spontaneous premature labor; contributory fetal or infant factors include "gigantism," hydramnion, prematurity, and congenital malformations. The maternal disease is involved both directly and as a remote cause of the complicating or contributory factors. Among the various factors; all but gigantism, prematurity and malformations predispose to death *in utero*, or stillbirth, rather than to neonatal loss. The probable correlations of these various factors with each other and with the time of fetal or infantile death is suggested in Fig. 1, (for the construction of which the reviewer has drawn upon the data of Peel and Oakley[45]).

The modifying influence of therapeutic measures upon infantile loss is considered in the section on Management. But it is necessary at this point to note that a therapeutic policy of premature termination of pregnancy (at or about the 36th week) lessens total infant wastage markedly, apparently by liberating the fetus from the baneful influences of the maternal disease and of the complications peculiar to the final months of gestation (see Tables 4 and 5).

2. *The Maternal Diabetes.* To the degree that diabetes may be responsible for overdevelopment of the fetus, or for toxemia and other complications

TABLE 3.—DIABETIC PREGNANCY

Relation Between Frequency of Toxemic Complications and Stillbirths

| | | *Frequency of Toxemia* | | | | | |
|---|---|---|---|---|---|---|---|
| *Source of Data* | *Pregnancies No.* | *Median* % | *Stillbirths* % | *High* % | *Stillbirths* % | *Low* % | *Stillbirths* % |
| British Clinics: | 599 | 17.0 | (25.1) | 19.0 | (29.4) | 10.6 | (11.3) |
| American Clinics: | 850 | 25.1 | (11.1) | 46.0 | (15.7) | 18.7 | (9.7) |

Note that the stillbirth rate varies directly, if not proportionally, with the incidence of preeclamptic toxemia.

TABLE 4.—DIABETIC PREGNANCY

Influence of Therapeutic Termination at 36th Week Upon Frequency of Maternal Complications

| | | *Pre-pregnancy Diabetes Established More Than 10 Years* | *Complications of Pregnancy* | |
|---|---|---|---|---|
| *Source of Data* | *Pregnancies No.* | % | *Hydramnion* % | *Toxemia* % |
| British Clinics: | | | | |
| No termination | 458 | 16.0 | 27.0 | 19.0 |
| Termination | 141 | 33.0 | 31.0 | 10.6 |
| American Clinics: | | | | |
| No termination | 266 | 11.0 | 5.6 | 33.5 |
| Termination | 584 | 42.0 | 10.3 | 21.2 |

FIG. 1. DIABETIC PREGNANCY: Causes and Nature of Fetal Loss. The numerals indicate the order of frequency with which the conditions listed in each column are encountered.

of pregnancy, it is easy to hold it accountable for fetal damage or loss. But a significant number of late fetal deaths of the intrauterine type are encountered in which no complications are present. In these, the maternal disease appears to be the direct or only possible cause of death. The nature of the lethal effect under these circumstances is obscure. According to most observers, the accidents under consideration cannot be correlated with severity or duration of the diabetes, though poor control appears to favor their occurrence[15,16,46]. There is an implication in several recent reports, moreover, that poor control of a continuous and "partial" type is more lethal than are occasional acute lapses featured by acidotic or hypoglycemic coma[45,61].

3. *Placental Hormonal Imbalances.* As is well known, White[23] has maintained for a number of years that fetal accidents and other complications of diabetic pregnancy are presaged and accompanied by quantitative abnormalities in the gestational metabolism of placental gonadotrophin, estrogen and pregnanediol. In this, she has extended certain earlier observations of the Smiths[55], which were based upon studies of pregnancy toxemia. Recently she has estimated, on the evidence of further assays and other considerations, that the hormonal abnormalities under consideration are present in 97% of pregnancies wherein the fetus or infant is lost[61].

White's observations have not yet been examined in other laboratories on any extensive scale, and such work as

TABLE 5.—DIABETIC PREGNANCY

Influence of Therapeutic Termination at 36th Week Upon Fetal Loss

| *Source of Data* | *Pregnancies* No. | *Fetal Loss* *Stillbirths* % | *Neonatal Deaths* % | *Total Fetal Loss* % |
|---|---|---|---|---|
| British Clinics: | | | | |
| No termination | 458 | 29.4 | 10.8 | 40.2 |
| Termination | 141 | 11.3 | 14.2 | 25.5 |
| American Clinics: | | | | |
| No termination | 266 | 16.2 | 6.4 | 22.6 |
| Termination | 584 | 8.8 | 8.7 | 17.5 |

Note that the lower fetal loss seen in early termination of diabetic pregnancy is accounted for by a lower number of stillbirths.

TABLE 6.—DIABETIC PREGNANCY

Influence of Mode of Delivery upon Fetal Loss
(Data of Peel and Oakley)

| *Mode of Delivery* | *Pregnancies* No. | *Fetal Loss* *Stillbirths* % | *Neonatal Deaths* % | *Total Fetal Loss* % |
|---|---|---|---|---|
| Spontaneous labor* | 137 | 17.8 | 18.6 | 36.4 |
| Induced labor* | 149 | 18.1 | 10.1 | 28.2 |
| Cesarean section | 213 | 1.4 | 14.6 | 16.0 |

* Fetus alive *in utero* at onset of labor.

has been done has yielded variable results. Thus, Peel and Oakley[45] have confirmed that hormonal abnormalities can be demonstrated in diabetic pregnancies which develop toxemia or hydramnios, or in which intrauterine death occurs. Loraine[29], on the other hand, has found chorionic gonadotrophin raised in 6 of 18 diabetic pregnancies, but under circumstances bearing no relation to such clinical phenomena as overweight baby, intrauterine death or toxemia. Similarly inconclusive findings are reported by Rubin *et al.*[53], and Keltz *et al.*[24].

The theoretical implications of White's work are of great interest, and have provoked much comment[15,49]. (Her recommendations with respect to hormonal therapy are considered below in the section on Management). The reviewer is one of those who believe, with White, that her findings reflect an overstimulation of the placenta (by some unknown factor), the ultimate effect of which is to bring about premature exhaustion or senesence of that organ. The fact that neither hormonal abnormalities nor histologic evidence of placental senesence can be demonstrated in some diabetic pregnancies may signify that there are fundamental differences in the pathogenesis of diabetes among different women[28,49]. Where hormonal abnormalties exist, however, White's concept provides plausible theoretical explanations for the development of such complications as toxemia, hydramnion, fetal gigantism, and fetal death *in utero*, with its predisposition to premature onset of labor.

4. *Gestational Toxemia.* Early observers were impressed not only by the frequency with which preeclamptic toxemia develops in the last trimester of diabetic pregnancy, but also by the frequency with which its appearance is attended or followed by intrauterine death of the fetus. There continues to be a correlation demonstrable between toxemia and stillbirths in diabetes when the combined statistics of all recently reported clinical studies are analysed as shown in Table 3. But the incidence of toxemia varies widely among the groups of cases reported from different clinics, ranging from 10%[45,49] to 50%[3,15,35,40], and those groups exhibiting high rates do not all show coincidentally high rates of fetal loss. As one studies the data, it is apparent that there must be considerable differences of practice between one center and another in the criteria utilized for establishing the diagnosis of this disorder.

The vascular damage that may be sustained in diabetic women prior to pregnancy is undoubtedly a provocative factor in the development of gestational toxemia. This is particularly apt to be the case among juvenile diabetics and those women whose disease has been present for some years (see Tables 2 and 4)[61]. Under such circumstances the onset of toxic symptoms may occur shortly after midpregnancy, and fetal loss is high. But both of the latter phenomena are also observable in nondiabetic women, given a similar background of prepregnancy maternal vascular disease or hypertension[7]. Where there is no such background, toxemia in nondiabetic women is characteristically a complication of the last weeks of gestation, and this is apparently also the case among diabetic women. But under these circumstances, the fetal loss is much higher in the diabetic than in the nondiabetic subject[15]. In view of this, the role of late gestational toxemia in fetal loss among diabetics, though important and proximate, is probably contributory rather than basic.

5. *Hydramnion.* The frequency of this complication in diabetic pregnancy and its significance in relation to infant

loss is emphasized by British workers[3,45]. In their experience, it appears to be closely associated with gestational toxemia, and with fetal gigantism and malformations. The infantile mortality encountered in its presence is presumably that of the associated conditions, plus the accidents of delivery peculiar to hydramnion itself, for example, malpresentations, and prolapse of fetal extremities or of the umbilical cord. Its development is apparently not related to maternal hyperglycemia, nor does examination of the amniotic fluid in these cases reveal an unusually high concentration of glucose[45].

6. *Fetal Gigantism.* This condition, estimated to be present in from 45 to 70% of diabetic pregnancies, was formerly a background factor in many fatal infantile birth injuries. The latter are now largely avoided by the premature termination of pregnancy with cesarean section or, in suitable circumstances, by the induction of premature labor. Nevertheless, early neonatal losses continue to be encountered among these large infants. Many of them are edematous at birth and, regardless of their excessive size or gestational age, exhibit characteristic weaknesses comparable to those seen in premature and erthryoblastotic infants[33, 34,37,45,49,61].

7. *Neonatal Hypoglycemia.* The plausible notion that early neonatal deaths among infants of diabetic mothers may be due to a hypoglycemia, provoked by an overactive level of pancreatic function established during intrauterine life, has been critically examined in recent years[45,47,48,49]. Serial samplings of infantile blood-sugar levels at frequent intervals following birth have confirmed that readings may be found as low as 20 or 30 mg. per 100 cc. during the first few hours, returning to normal only rather slowly during the first week of life. This phenomenon, however, is also demonstrable to some degree among all newborn infants, and it is not accompanied by the clinical distress attending hypoglycemia in adults[25]. Only to the extent, therefore, that hypoglycemia may be more severe, or may develop more precipitously, among the newborn of diabetic than of nondiabetic mothers would it appear to be of significance as a factor in neonatal morbidity or death. The evidence on this point is conflicting, but the bulk of it does not support the concept under consideration[45,47].

8. *Congenital Malformations.* Congenital anomalies of the fetus in diabetic pregnancy continue to be noted in numbers exceeding those which would normally be expected[45,61]. With respect to fetal loss, however, the importance of these malformations *per se* is probably small. In one large American study of diabetic women, they were present as a factor in only 3% of infantile deaths[61]. Similarly, British observations indicate that their role in these losses is confined largely to the small numbers of late neonatal deaths involved in the total combined fetal and infantile mortality of diabetic pregnancy[45].

Diagnosis. The recent literature contains relatively little information to add to the discussion of this subject recorded by Eastman[10]. The expectant mother who has been diabetic from childhood generally presents no problem of diagnosis. In other circumstances, an obstetric history of the occurrence of complications suggestive of prediabetes should warn the alert obstetrician of the possible presence or development of diabetes in the current pregnancy. Recent studies concerning the significance of glycosuria in pregnancy have been reviewed by Moss and Mulholland[38], and others[1,5, 19,21,58].

MANAGEMENT OF DIABETIC PREGNANCY. 1. *General Considerations*—All recent contributors to this field emphasize the advantages to the diabetic mother and her infant of (a) close collaboration between her obstetrician and her medical adviser; (b) careful check of her gestational status, and of the stabilization of her diabetes, at frequent intervals during the prepartal period (with occasional hospitalization as necessary for this purpose); and (c) early hospitalization when complications threaten or when the time for delivery nears.

2. *Diet and Insulin Therapy.* The principal objective of dietary planning in diabetic pregnancy is considered to be the achievement of an optimal rate and degree of gain in maternal weight, having due regard to the special protein requirements of gestation and the patient's limited capacity for handling glucose. Thus, total weight gain should not exceed about 11 kilograms (or 25 pounds), and this gain should be held within even lower limits if the prepregnancy weight is already excessive. A minimum of 1 to 1.5 gm. of protein per kilogram of body weight per day is indicated under all circumstances. Additional fat and carbohydrates are then provided in the usual 1:2 ratio (by weight) to make up a total dietary intake not exceeding in value about 30 calories per kilogram of body weight per day[49,61].

It is advocated that maternal diabetes be managed under a plan of "clinical control" rather than one of strict "chemical control"[15,49]. Because of the normal tendency to a lowering of the renal threshold for glucose excretion during gestation, attempts to keep the mother's urine free of sugar at all times may invite attacks of hypoglycemia, or depress her sense of well-being to such a degree as to alienate her willingness to cooperate in other phases of management[49].

Special watchfulness is necessary for detecting changes in insulin requirements during the last trimester of diabetic pregnancy. As the time for labor or delivery approaches, moreover, the use of regular insulin must replace that of long-acting insulin because of the unavoidable uncertainties of feeding programs and schedules during these events, and of the rapid changes in insulin-requirements that may follow them[46,61].

3. *Hormonal Therapy.* Adjunctive treatment of the diabetic pregnant woman with increasing dosages of estrogen and progesterone, starting in the early months of gestation, continues to be recommended by White [61,62]. She finds that these substances (a) raise (by addition or substitution) the levels of circulating estrogen and pregnanediol in pregnant women, and (b) by so doing, contribute to fetal wellbeing.

Peel and Oakley[45], and Loraine[29] have recently confirmed White's findings regarding the effects of hormonal therapy upon the maternal hormonal metabolism. But no unanimity of opinion exists among those who have attempted to examine the clinical value of White's therapeutic regimen. Palmer *et al.*[40] report a fetal and infant salvage of 83% in a group of women treated with stilbestrol and progesterone. The Smiths[56] find stilbestrol therapy to be useful not only in diabetic but also in normal pregnancy. British clinicians, however, have thus far been unimpressed with results achieved by the administration of stilbestrol in diabetes[3,45].

Skepticism concerning the claimed value of hormonal therapy has been recorded by those who feel that a comparably favorable fetal salvage is currently obtainable without its use[15,49].

Critics point out, with considerable logic, that any good results obtained in both White's and their own experiences are probably attributable to careful control of the maternal diabetes, therapeutic premature termination of pregnancy, and the liberal employment of cesarean section for delivery. The reviewer, acknowledging the force of these arguments, nevertheless feels that final judgment in this controversial matter should be reserved pending the accumulation of further evidence. In justice to White, it should be borne in mind that her views have been developed from personal experience with a tremendous number of patients, over half of whom have been juvenile diabetics exhibiting serious problems. Her conclusions therefore deserve careful consideration.

It should be noted that hormonal therapy in diabetic pregnancy may evoke undesirable side effects. One type of stilbestrol preparation used for parenteral injection has apparently been responsible for the development of endometrial hyperplasia and uterine bleeding during the postpartal period[31,61]. An instance of acute thrombocytopenic purpura following massive hormone therapy has been reported[51].

4. *Premature Termination of Pregnancy.* Because the risk of intrauterine death of the fetus in diabetic pregnancies rises gradually from the 32nd to the 40th week, and after 36 weeks exceeds the risk of neonatal death[45], there has been a growing tendency in various centers to terminate gestation at or about the 36th week in the absence of special indications for earlier or later interference[40,45,46,49,61]. The favorable effects of this policy on fetal salvage, as reflected in the results obtained in those clinics wherein it has been applied to a majority of patients, is shown in Tables 4 and 5. The figures confirm that the saving of fetal life noted is accomplished by a reduction in the frequency of stillbirths, particularly those due to early fetal death *in utero*. They also show a coincidental reduction in the number of late complications of pregnancy among patients managed under this policy.

5. *Mode of Delivery.* Cesarean section has been increasingly favored in recent years as a method of delivery in diabetic pregnancy[40,45,46,49,61]. Observers have long noted that spontaneous labor in these pregnancies is apt to be prolonged, and in addition, that the fetus withstands the normal buffetings of labor and vaginal delivery poorly[45]. Moreover, when therapeutic termination of pregnancy is deemed necessary, either at term or (especially) at an earlier period, labor may be difficult to induce unless the patient is a multipara and the condition of her uterine cervix is favorable. In delays attending the onset or course of labor, the maternal diabetes is difficult to control.

Given a living fetus *in utero*, the risks confronting it in different methods of delivery have been examined by Peel and Oakley[45] as shown in Table 6. It will be seen that 1 fetus in 6 suffers an intrapartal death during labor or delivery *per vaginam*, and that this loss occurs regardless of whether the labor be spontaneous or induced. On the other hand, only 1 fetus in 70 is lost during delivery by cesarean section. Given a live birth, neonatal loss is about the same whether the child has been delivered *per vaginam* or by section. It is of interest that following cesarean section, if performed at any time from the 36th week of gestation onward, the risk of neonatal loss of the infant is the same regardless of its maturity[45].

MANAGEMENT OF THE NEWBORN INFANT. In diabetic pregnancy, the delivery of a living baby, by whatever method, is by no means the end of the

road in the quest of a healthy child[45]. Regardless of the infant's size, gestational maturity or condition at birth, signs of respiratory embarrassment will often develop within a few hours, and lead to death within the first day or two of life.

Successful management of the newborn infant demands, therefore, that it be cared for as if it were a premature baby irrespective of its actual age[49,61]. The upper respiratory passages should be cleared promptly at birth, and kept cleared during the first days of life. Particularly is this precaution advised for infants born by cesarean section; in such infants the further precaution of aspirating the stomach at birth is urged[11]. The infant should be kept in a constant temperature incubator, under oxygen, and in a position to favor postural drainage of the respiratory passages, until its condition warrants removal to an open crib.

In view of the frequent presence of edema, and in the light of other considerations, most pediatricians do not favor attempts at oral feeding of these infants during the first day or two of life. Reis *et al.*[49], however, believe that the hypoglycemia which is generally present should be combatted by feeding glucose in small concentrated quantities.

Whatever the factor may be that kills so many babies within a few hours of their birth, it merely retards the progress of the remainder for a comparatively short time. Those infants which surmount the early dangers may be slow, lethargic and difficult to feed and rear during the first few weeks. But once this period is passed, their further progress does not differ in any respect from that of healthy infants[45].

**Comment and Summary.** Despite the considerable improvement in fetal and infant salvage that has been noted in diabetic pregnancy in recent years, fetal loss continues to be a serious and important aspect of this condition. The gains that have been made have naturally been due to the great advances that have been taking place coincidentally in the fields of internal medicine, obstetrics and pediatrics. But much of the late progress that has been recorded has been attributable to a widening adoption of the policy of removing the fetus from its unhealthy environment in the mother at as early a point in gestation as will ensure it a reasonably good outlook for extrauterine survival. This strategy of circumventing the evil influence of diabetes and its complications upon the fetus *in utero* has been necessary because the basic nature of that influence remains poorly understood or out of range of direct therapeutic attack. Until these difficulties are surmounted, prospects for further substantial improvement in fetal salvage are not likely to be bright.

The quest for an understanding of the deleterious action of diabetes upon pregnancy has meanwhile provided some suggestions concerning its essential nature. Thus, the conclusion appears inescapable that the primary fetal changes are caused by a perversion or overactivity of maternal pituitary function. The fetal overdevelopment that is so characteristic resembles, according to White and others, some of the features of growth exhibited by juvenile diabetics during their adolescent years. The visceral manifestations of this disorderly fetal growth have been likened by H. C. Miller to those seen in acromegaly. Moreover, the humoral factor (or factors) through which they are doubtless mediated appear to bear mainly upon the already developing or fertilized ovum rather than upon the preconceptional maternal germ plasm. Circumstantial evidence in support of this view is the fact that,

whereas the rate of spontaneous early abortion in diabetic pregnancy is barely twice the expected or "normal" one, the incidence of congenital malformations among viable fetuses is at least 6 times that encountered in children of normal mothers. Since it is generally held that most aborted fetuses are blighted ova to begin with, this discrepancy suggests that the products of conception of diabetic mothers are not less healthy than those of normal mothers, but are more apt to become malformed as a result of unfavorable environmental conditions *in utero*. The pathogenesis here might well be analogous to that seen in the expectant mother who contracts rubella during the early months of gestation.

Whatever it is that provokes fetal overdevelopment and malformations in diabetic pregnancy, the same factors also appear to "exhaust" the placenta prematurely during the later months of gestation. In the absence of any other hypothesis, it is difficult to avoid the supposition that it is this course of events which causes so many fetal deaths *in utero* at that period, either directly or by provoking the appearance of the added complication of preeclamptic toxemia. In a number of instances this degenerative phase and the appearance of toxemia may both be hastened by the presence of chronic maternal vascular disease or hypertension dating back to the preconceptional period. The abnormalities in excretion of gonadotrophin, estrogen and pregnanediol noted by White and others apparently reflect the status of placental function during this phase of deterioration.

Hormonal therapy in diabetic pregnancy has no significant influence upon the frequency with which fetal overdevelopment is encountered. It is thus presumably without much effect upon any primary growth-promoting action which the disease may exert upon the fetus. As White herself has emphasized, its principal purpose is to buttress the failing placental production of hormones that presages the critical period of pregnancy in the diabetic. Hence it aims, like all other currently available therapeutic measures must, at neutralizing or circumventing ovular damage rather than at exorcizing the primary factors responsible for that damage. But as those factors may also be involved in the pathogenesis of the maternal diabetes, any hope of attacking them directly in the interest of the fetus may have to await the ultimate discovery of a curative therapy for diabetes mellitus itself.

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PROCEEDINGS OF
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**The Relation of Amylase Activity to Specific Gravity in Canine Pancreatic Juice.** F. P. Brooks, M.D., (Department of Physiology, Jefferson Medical College.) Pancreatic juice was obtained from unanesthetized healthy dogs equipped with duodenal and gastric fistulae. Tenth-normal hydrochloric acid, oleic acid and peptone solutions were used as stimuli to obtain juice of specific gravity ranging from 1.009 to 1.022. Amylase activity was determined by the turbidimetric method of Waldron with the following modifications: varying dilutions of pancreatic juice varying from 1:100 to 1:600 were employed so that the substrate remaining undigested at the end of 3 minutes fell between 60 and 90%. The velocity constant was calculated over the time interval 0 to 3 minutes and for juices diluted beyond 1:100, the "K" was multiplied by the dilution factor. Tenth-molar sodium chloride was added to the diluting buffer solution in the ratio of 1:4. The water bath temperature was maintained at 30°C. Specific gravity was determined gravimetrically.

A correlation coefficient based on 52 observations was calculated as .91 within 99% fiducial limits of .82 to .92. The regression equation was $y = 64.915x - 65.438$. The regression coefficient was 64.915 with 95% fiducial limits of 56.620 to 73.210. The standard deviation from regression was .012.

Similar observations based on 6 determinations on each of 2 dogs on the same day suggested an even close correlation, but were not statistically significant.

Therefore, amylase activity is closely related to specific gravity and under these conditions the specific gravity may be used as indication of amylase activity. These observations support the theory of parallel secretion of pancreatic enzymes.

**Unusual Features in Hemoglobin and Stercobilin Metabolism in Splenectomized Dogs, Disclosed by Labeling with Glycine-2-$C^{14}$.** David L. Drabkin, M.D., Ashton Graybiel, M.D., J. K. Colehour, M.S., Vera Usdin, Ph.D., Anna May Dych, B.A., and Karen L. Miller, B.A. (Dept. of Physiol. Chem., Grad. School of Med., Univ. of Penna. and U.S. Naval School of Aviation Med., Pensacola). Glycine-2-$C^{14}$ (radioactive, methylene or alpha carbon labeled glycine) was administered to 6 thoroughbred Beagle hounds of the same age, 3 of them splenectomized 8 months earlier, and the labeling of hemoglobin and stercobilin was followed during a period of 150 days. Paired litter mates were used, one intact, the other splenectomized; one pair being kept at sea level, the others at a simulated altitude of 16,000 feet. Terminally, the animals were sacrificed and individual tissues removed for the isolation of myoglobin and cytochrome *c* to determine the radioactivities also of these chromoproteins.

Both splenectomized and intact normal dogs respond to the anoxia of high altitude with an increase in red cells and hemoglobin, which in the intact dog is at least partly owing to the production of new cells (Drabkin, D. L., and Graybiel, A., Fed Proc. *10*, 177,

1951). Nevertheless, in the present experiments the patterns of hemoglobin and stercobilin (bile pigment) labeling in the splenectomized animals, at sea level as well as at altitude, differed significantly from those in the intact dogs.

The curve of hemin labeling against time in the splenectomized dogs exhibited a less marked peak at 20 days than the normal, the degree of labeling was lower, and the decline in activity from 20 days on approached the pattern characteristic of random red-cell destruction. The latter was not fully explainable by a dilution effect due to more rapid new red-cell production. However, if the phenomenon were owing to greater red-cell breakdown, this was not reflected in anemia or in the output of stercobilin, whose pattern of labeling was strikingly abnormal.

Splenectomy had no consistent effect on the ratio of globin and hemin radioactivity. In all the animals studied the labeling of globin was parallel with that of the hemin. From the degree of hemin and globin labeling a tentative deduction may be drawn that both components are simultaneously biosynthesized from their precursors.

The unusual patterns of hemoglobin and particularly bile pigment labeling suggest the possibility of the existence of a hitherto unrecognized or unexplored function of the spleen in the metabolism of red cells and hemoglobin.

**Observations on the CO Pulmonary Diffusing Capacity.** R. E. FORSTER, W. S. FOWLER, B. VAN LINGEN and D. V. BATES. (Dept. of Physiol. & Pharmacol., Graduate School of Medicine, U. of Pa.). Marie Krogh, in her brilliant paper on the use of CO to measure the diffusing capacity of the lung (J. Physiol., 49: 271, 1915) made a number of important assumptions. Of these we have investigated four, namely (a) that following inspiration of a gas containing CO, the initial CO concentration is similar in all volumes of the lung gas; (b) that two successive expired alveolar gas samples contain the same proportional contributions from all parts of the lung; (c) that the CO diffusing capacity/lung volume is constant throughout the lung; and (d) that the pulmonary capillary blood $P_{B_{CO}}$ is negligible. Uniformity of ventilation was studied by following the He or $N_2$ concentration in expired gas with a rapidly recording mass spectrometer (90% response 0.04 seconds). CO concentration in the gas samples was measured with an infra-red absorption detector, with an accuracy of $\pm$ 4% as used.

It was found that alveolar ventilation and emptying sequence were uneven, so that assumptions (a) and (b) were incorrect. The expired alveolar CO concentration was not an exponential function of the time the gas had spent in the lung. There are a variety of possible explanations for this result, the most probable of which is that the diffusing capacity/lung volume is not constant throughout the lung, making assumption (c) incorrect. The rate of loss of CO was much greater when $P_{A_{O_2}}$ — 40 mm. Hg than when air was inspired ($P_{A_{O_2}}$ — mm. Hg). This suggests that assumption (d) was incorrect, and that $P_{B_{CO}}$ is significantly greater than zero, during air breathing.

**Studies of Steroid Antagonism. I. Local Inhibition by Estrone of the Comb Stimulating Action of Testosterone Propionate.** JOHN E. MARTIN, V.M.D., JOHN H. GRAVES, D.V.M., and F. C. DOHAN, M.D. (Department of Physiology and Pharmacology and Department of Anatomy, School of Veterinary Medicine, and the Department of Medicine, School of Medicine, University of Pennsylvania). The object of this study was to determine whether

estrogens inhibit the comb-stimulating action of androgens in capons by acting at the target tissue level. Combs of white Leghorn capons were surgically separated into two entirely separate half-combs. Testosterone propionate in a daily dose of 2 gamma was applied to both half-combs and simultaneous applications of various doses of estrone were made to one. The steroids were applied for 5 days. Half-combs treated with estrone in daily doses of 100 or 200 gamma, but not with 80 or 160 gamma, grew significantly less than their paired controls receiving only testosterone propionate. Histological development of the cockerel-type comb occurred in half-combs receiving only testosterone propionate, but the development was markedly depressed in the adjacent half-comb treated with the estrone - testosterone propionate mixture. It is concluded that under the conditions of this experiment estrone acted by antagonizing the action of testosterone propionate at the target tissue level. Relative proportions of the hormones present seem to be an important feature in determining the type of response of the androgen-estrogen mixture.

**A Method for Evaluating the Distensibility of Blood Vessels and its Application to the Veins and Arteries.** LYSLE H. PETERSON, M.D., (Department of Physiology, University of Pennsylvania.)

The measurement of rate of change of volume within the intact vascular system has always been beset with severe limitations, while it has become relatively easy to measure, accurately, pressure changes. For many years physiologists have been attempting to relate the two, namely, $P/V = f$. The value of f has been the subject of a voluminous literature due to the fact that the vascular tree has by no means a single degree of freedom. This is amply demonstrated by the inconstancy of pulse wave velocity and pulse wave contour as they travel toward the periphery. A method is hereby presented which provides an absolute value of f for each increment of P and V.

The method consists of the introduction of a known volume change, with a constant time slope lasting 0.1 to 0.2 sec., into the vascular system. The resultant pressure curve is integrated relative to the volume curve. This method has been applied to the vena cava in an effort to investigate the activity of the "venomotor" system. Results of this work have demonstrated that the inferior vena cava is capable of altering its distensibility by 10 to 15 times under the influence of autonomic activity and hemorrhage. At normal levels of pressure the veins are undistended. Parasympathetic stimulation causes the distensibility to increase and the vessels become more elastomeric. Sympathetic stimulation and hemorrhage cause the vessels to behave more as rigid tubes. Preliminary applications of this method, within the arterial system, have also shown it to be of promise for the calculation of stroke volume.

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# BOOK REVIEWS AND NOTICES

CLINICAL TROPICAL MEDICINE. R. B. H. GRADWOHL, M.D., Editor-in-Chief; LUIS BENITEZ SOTO, M.D., and OSCAR FELSENFIELD, M.D., Editors. Pp. 1647; 473 ills.; 6 color plates. St. Louis: C. V. Mosby Co., 1951. Price, $22.50.

THE editors point out that this book is intended as a guide for those practicing medicine in the tropics as well as for those in temperate zones, who must recognize there the diseases originating in or transmitted from the tropics.

The book is the most important attempt, in English, to cover in detail this field since the encyclopedic text of Castellani and Chalmers. It differs from that classic of a generation ago in that its emphasis is clinical, with less detail on parasitology, classification and description of vectors of disease; also in that it is a multiple-author project, written by 57 men; 23 from the Continental United States, the others from 10 countries and islands in this hemisphere and from England, Holland, Spain, Egypt and India.

Today so few diseases are peculiar to the tropics and so many occur in varying preponderance in different areas, tropical and temperate, that the editors solved the dilemma of what diseases to consider by including many not necessarily tropical, largely or in part, and some that are well covered in ordinary textbooks of medicine: for example, Japanese B. encephalitis, rickettsial pox, tularemia, equine encephalomyelitis, trichinosis and brucellosis. There are good chapters on hygiene in the tropics, preventive medicine and rural hygiene services in sparsely settled tropical countries, and on practical laboratory procedures, including hematology, histologic technique and formulae of reagents, solutions, stains and culture media. There are many good illustrations. In the main, the editors have achieved their objective and produced a valuable addition to the literature on the subject.

There are some defects that should be noted, since they can be remedied in the future editions which the work deserves. It took too long to get 57 men to get their chapters written, so that many parts are already out-of-date. Of 73 chapters, only 3 have references as late as 1950; in 6, the most recent citations are dated 1949; in 14, they are 1948; and the rest have no reference later than 1947. Diasone is not mentioned in the article on leprosy; nor the usefulness of Hetrazan in larva migrans; nor Camaquine or Primaquine in the treatment of malaria. Emetine is not now preferred in the treatment of hepatic amebiasis. There is no mention of the increased toxicity of 8-aminoquinoline drugs in malaria therapy if Quinicrine, the sulfonamides, or Paludrine are given simultaneously. There is needed a statement on the classification of the Trypanosomidae. There is no mention of the milder forms of Weil's Disease, recently recognized. It would have been more logical to have the chapters on Pinta and Yaws (treponemal infections) together, rather than separate them by the chapters on the relapsing fevers, the leptospiral diseases and rat bite fever. There is a wide diversity in the documentation of each chapter with references. A few chapters have almost no references, yet one chapter a page and a half long has a page and a half of references. Finally, the book is too expensive for medical students. These are not destructive criticisms. For a first edition, there are amazingly few serious defects. There are no omissions and few duplications. The book is heartily recommended. R. K.

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AN INTEGRATED PRACTICE OF MEDICINE. PROGRESS VOLUME, MODERN DEVELOPMENTS IN THERAPEUTICS AND METHODS OF TREATMENT. Volume 5. By HAROLD THOMAS HYMAN, M.D. Pp. 734. Philadelphia: W. B. Saunders Co., 1950. Price, $10.00.

THIS progress volume brings up-to-date the material presented in the original four volumes of Integrated Practice of Medicine. The items are alphabetically arranged, easily accessible and well presented. Of particular value, and something new in supplementary volumes of this type, is the inclusion of the original index for the first four volumes in the back of this progress volume, together with an index to the new material in the progress volume in separate pages of a different color. This greatly facilitates the availability of all the material. R. K.

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SAVILL'S SYSTEM OF CLINICAL MEDICINE. Edited by E. C. WARNER, M.D., F.R.C.P. 13th ed. Pp. 1198; 195 ills.; 7 colored plates. Baltimore: Williams & Wilkins, 1950. Price, $7.00.

FOR over 40 years this has been a standard British text. It differs from other textbooks of medicine in its approach: instead of a series

of descriptions of diseases, the presentation is from the standpoint of what the physician finds at the bedside; for example, acute abdominal pain: its possible causes. The present editor and his 17 associate contributors have brought the volume up-to-date and adhered to the original plan. Problems of differential diagnosis are particularly well-handled. Drugs conform to the British Pharmacopoeia. Dosages, unfortunately, are a mixture of English and metric systems.

R. K.

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A Textbook of Orthopedics. By M. Beckett Howorth, M.D., Clin. Prof. of Orthop. Surg., New York Univ. Post-Grad. Med. School. Pp. 1,110; 463 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $16.00.

In a single text Dr. Howorth has covered all aspects of orthopedics, including its history, the anatomy of the neuromuscular system, the principles of examination and diagnosis and fundamentals of treatment and finally regional orthopedics. To do this with completeness in 1,110 pages is well nigh impossible. The material covered, however, is well presented. Illustrations are not too copious, and in my opinion, lacking on some of the more common orthopedic problems. The section on fractures, which incidentally totals a mere 67 pages is, of necessity, almost done in outline fashion, and illustrations here are most scant.

It is certainly apparent that the author has a broad and complete knowledge of his subject. His presentation is lucid. The orthopedist should have it as a part of his library, both as a text and a reference source, since the bibliography Dr. Howorth has compiled will probably be the envy of many previous authors of orthopedic texts. A. S.

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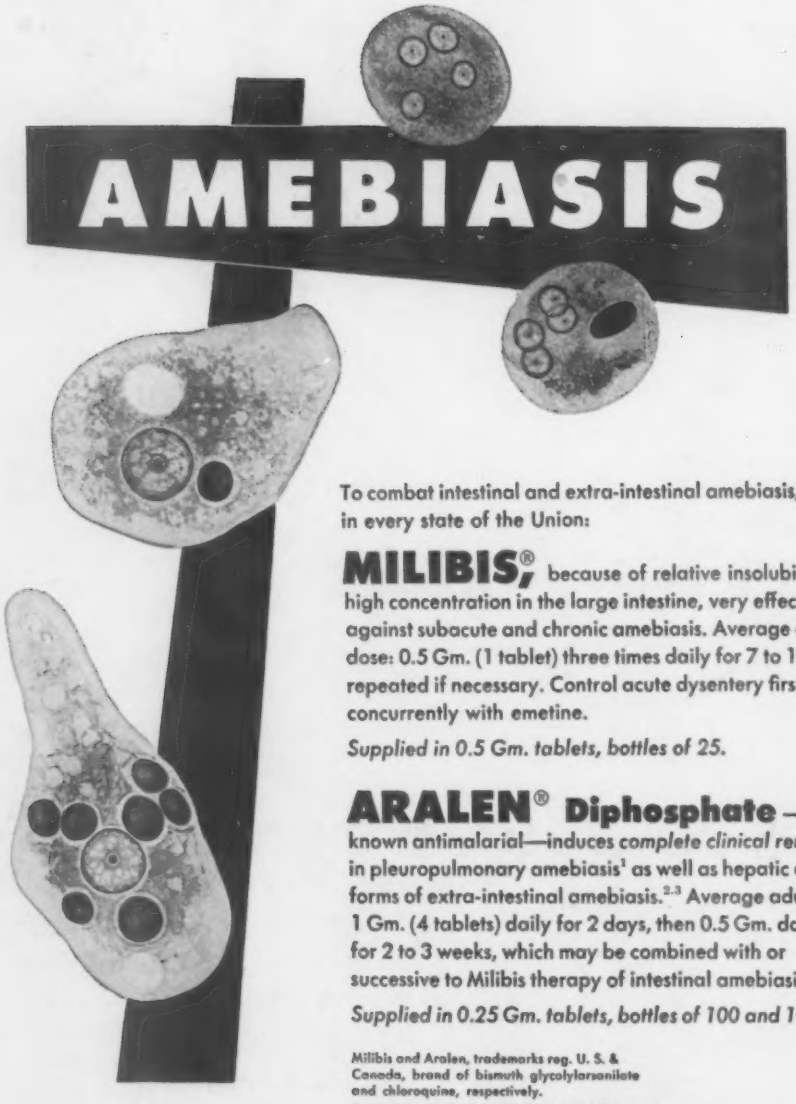
| theophylline | 2 gr. |
| ephedrine | 3/8 gr. |
| phenobarbital | 1/8 gr. |

*in boxes of 24, 120 and 1000 tablets*

**Tedral**

CHILCOTT *Laboratories* DIVISION OF The Maltine Company MORRIS PLAINS, NEW JERSEY




To combat intestinal and extra-intestinal amebiasis, found in every state of the Union:

**MILIBIS,®** because of relative insolubility, assures high concentration in the large intestine, very effective against subacute and chronic amebiasis. Average adult dose: 0.5 Gm. (1 tablet) three times daily for 7 to 10 days, repeated if necessary. Control acute dysentery first or concurrently with emetine.

*Supplied in 0.5 Gm. tablets, bottles of 25.*

**ARALEN® Diphosphate** —the well known antimalarial—induces *complete clinical remission* in pleuropulmonary amebiasis[1] as well as hepatic and other forms of extra-intestinal amebiasis.[2,3] Average adult dose: 1 Gm. (4 tablets) daily for 2 days, then 0.5 Gm. daily for 2 to 3 weeks, which may be combined with or successive to Milibis therapy of intestinal amebiasis.

*Supplied in 0.25 Gm. tablets, bottles of 100 and 1000.*

Milibis and Aralen, trademarks reg. U. S. & Canada, brand of bismuth glycolylarsanilate and chloroquine, respectively.

1. Lindsay, A. E., Gossard, W. H., and Chapman, J. S.: *Dis. Chest*, 20:533, Nov., 1951.
2. Conan, N. J., Jr.: *Am. Jour. Med.*, 6:309, Mar., 1949.
3. Emmett, J.: *J.A.M.A.*, 141:22, Sept. 3, 1949.

***Illustrated brochure on request.***

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